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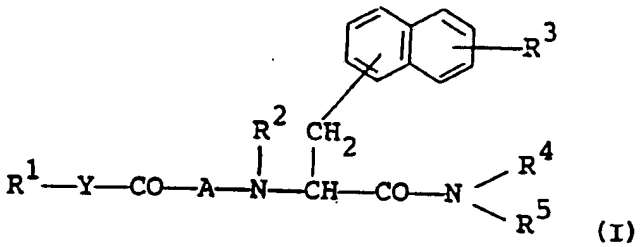
(54) Title: PEPTIDES WITH TACHYKININ ANTAGONIST ACTIVITY



(I)

(57) Abstract

The object compounds of the present invention can be represented by general formula (I), wherein R^1 is lower alkyl, etc., R^2 is hydrogen, etc., R^3 is hydrogen, etc., R^4 is lower alkyl, etc., R^5 is ar(lower)alkyl, etc., A is an amino acid residue; and Y is bond, etc. The object compounds (I) and pharmaceutically acceptable salt thereof have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin A antagonism or neurokinin B antagonism.

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DESCRIPTION

PEPTIDES WITH TACHYKININ ANTAGONIST ACTIVITY

Technical Field

The present invention relates to new peptide compounds and pharmaceutically acceptable salt thereof.

More particularly, it relates to new peptide compounds and pharmaceutically acceptable salts thereof which have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin A antagonism, neurokinin B antagonism, and the like, to processes for preparation thereof, to pharmaceutical composition comprising the same, and to a use of the same as a medicament.

One object of the present invention is to provide new and useful peptide compounds and pharmaceutically acceptable salts thereof which have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin A antagonism, neurokinin B antagonism, and the like.

Another object of the present invention is to provide processes for the preparation of said peptide compounds and salts thereof.

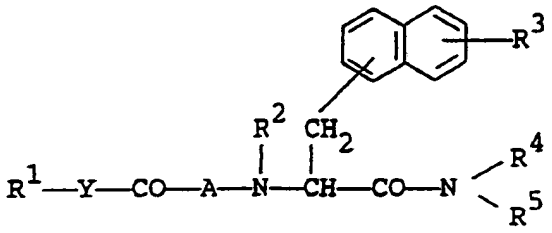
A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said peptide compounds and pharmaceutically acceptable salts thereof.

Still further object of the present invention is to provide a use of said peptide compound or a pharmaceutically acceptable salt thereof as tachykinin antagonist, especially substance P antagonist, neurokinin A antagonist or neurokinin B antagonist, useful for

treating or preventing tachykinin mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis, cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like; pains or aches (e.g., migraine, headache, toothache, cancerous pain, back pain, etc.); and the like in human being or animals.

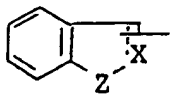
Disclosure of Invention

The object compounds of the present invention can be represented by the following general formula (I).



wherein R^1 is lower alkyl, aryl, ar(lower)alkyl, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, or a group of the formula :

pyrazolopyridyl, quinolyl, or a group of the formula :



wherein the symbol of a line and dotted line is a single bond or a double bond,
X is CH or N, and
Z is O, S or NH,
each of which may have suitable substituent(s);

R^2 is hydrogen or lower alkyl;

R^3 is hydrogen or suitable substituent;

R^4 is lower alkyl which may have suitable substituent(s), and

R^5 is ar(lower)alkyl which may have suitable substituent(s) or pyridyl(lower)alkyl, or

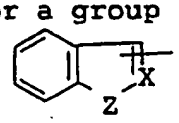
R^4 and R^5 are linked together to form benzene-condensed lower alkylene;

A is an amino acid residue which may have suitable substituent(s); and

Y is bond, lower alkylene, lower alkenylene or lower alkylimino,

provided that when

R^1 is aryl, or a group of the formula :



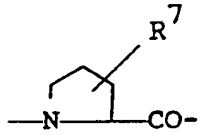
wherein X is as defined above, and
Z is O or N-R^6_a,
in which R^6_a is hydrogen or lower alkyl,

R^2 is hydrogen,

R^4 is lower alkyl which may have suitable substituent(s),

R^6 is ar(lower)alkyl which may have suitable substituent(s),

A is group of the formula :



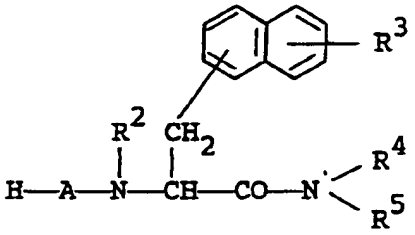
wherein R^7 is hydoxy or lower alkoxy, and

Y is bond or lower alkenylene, then

R^3 is suitable substituent.

According to the present invention, the new peptide compounds (I) can be prepared by processes which are illustrated in the following schemes.

Process 1



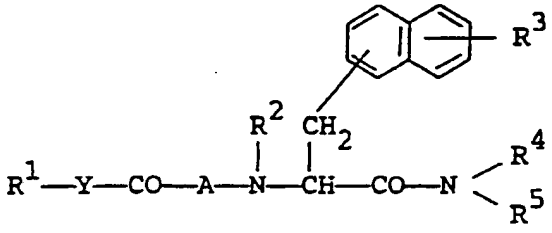
(II)

or its reactive derivative at the amino group or a salt thereof

$R^1 - Y - COOH$

(III)

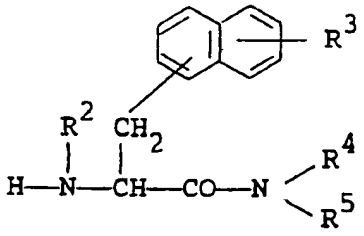
or its reactive derivative at the carboxy group or a salt thereof



(I)

or a salt thereof

Process 2



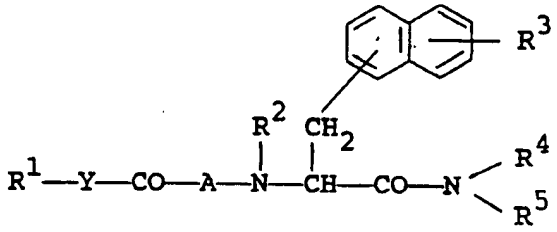
(IV)

or its reactive derivative at the amino group or a salt thereof

R^1-Y-CO-A-OH

(V)

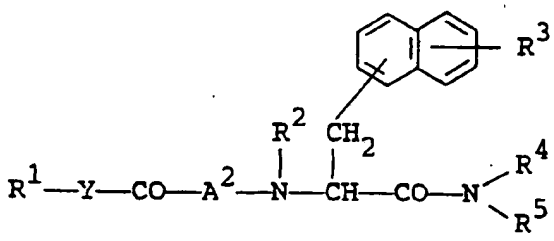
or its reactive derivative at the carboxy group or a salt thereof



(I)

or a salt thereof

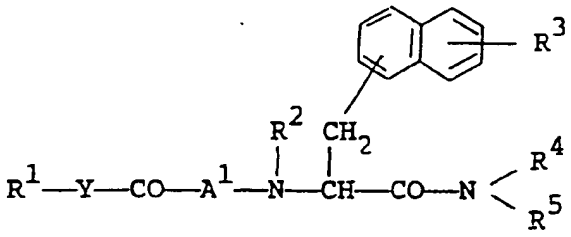
Process 3



(I-a)

or a salt thereof

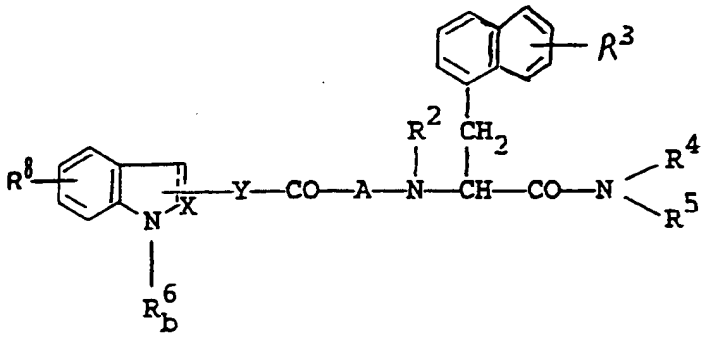
Elimination of the amino, hydroxy and/or carboxy protective group



(I-b)

or a salt thereof

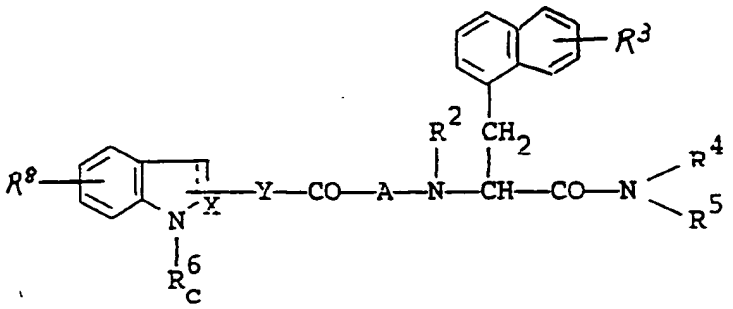
Process 4



Elimination of the carboxy or amino protective group

(I-c)

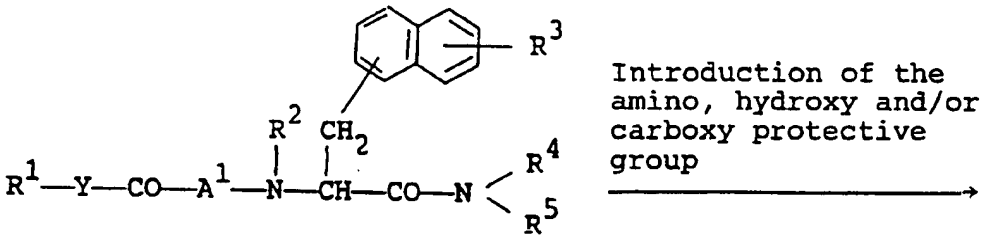
or a salt thereof



(I-d)

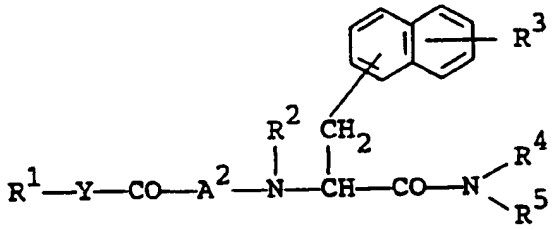
or a salt thereof

Process 5



(I-b)

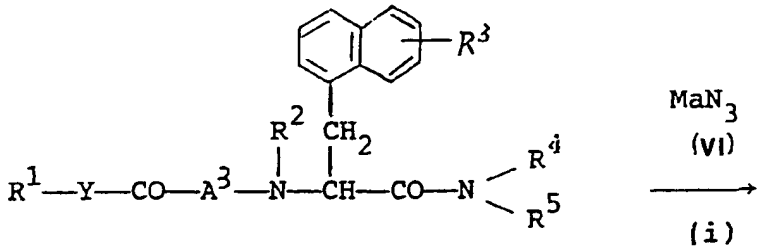
or its reactive derivative at the amino, hydroxy and/or carboxy group or a salt thereof



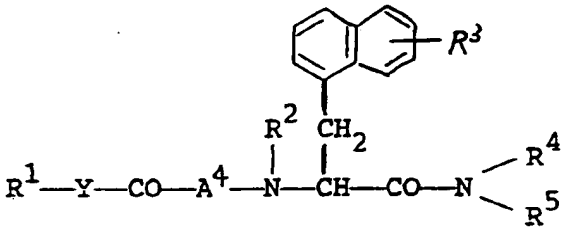
(I-a)

or a salt thereof

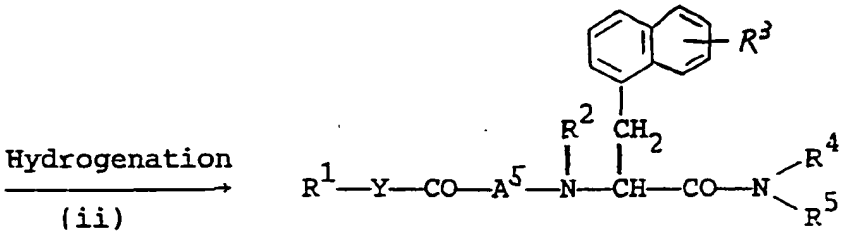
Process 6



(I-e)
or a salt thereof

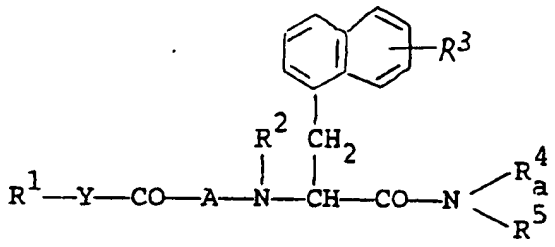


(I-f)
or a salt thereof



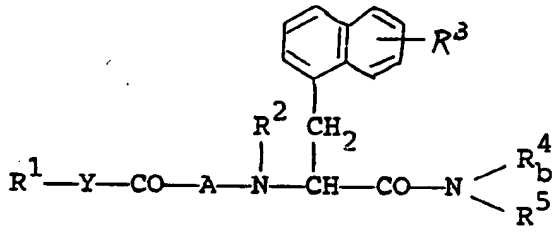
(I-g)
or a salt thereof

Process 7



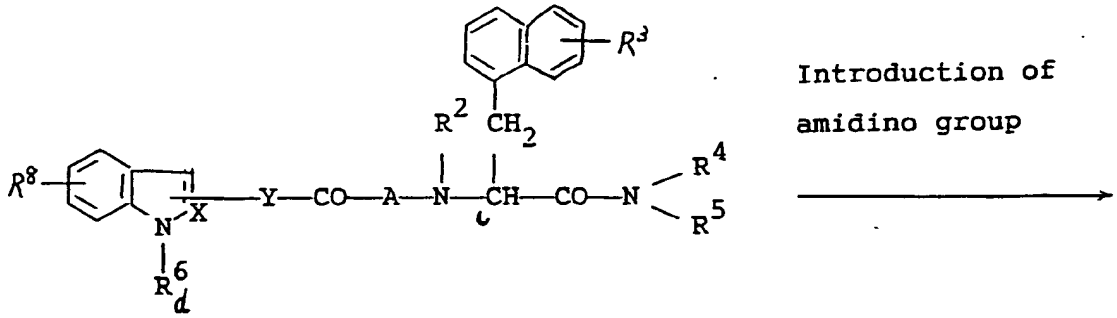
Elimination of the carboxy protective group

(I-h)
or a salt thereof

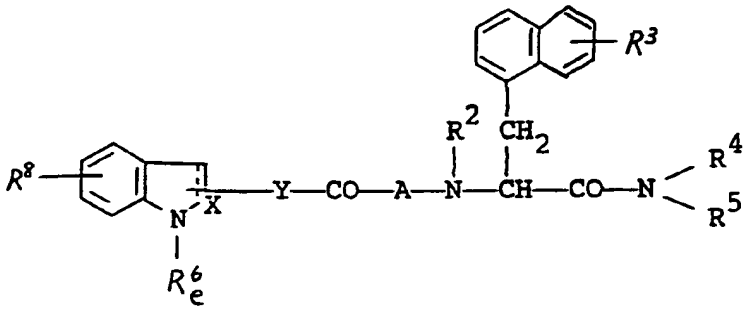


(I-i)
or a salt thereof

Process 8



(I-j)
or a salt thereof



(I-k)
or a salt thereof

wherein R^1, R^2, R^3, R^4, R^5, A, X and Y are each as defined above,

R^{4a} is protected carboxy (lower) alkyl,

R^{4}_{b} is carboxy (lower) alkyl,

R^{5}_{b} is protected carboxy (lower) alkyl or protected amino (lower) alkyl,

R^{5}_{c} is carboxy (lower) alkyl or amino (lower) alkyl,

R^{6}_{d} is amino (lower) alkyl,

R^{6}_{e} is guanidino (lower) alkyl,

R^{8} is hydrogen or halogen,

A^{1} is an amino acid residue containing an amino, a hydroxy and/or a carboxy,

A^{2} is an amino acid residue containing a protected amino, a protected hydroxy and/or a protected carboxy,

A^{3} is an amino acid residue containing a sulfonyloxy which has a suitable substituent,

A^{4} is an amino acid residue containing an azido,

A^{5} is an amino acid residue containing an amino,

Ma is an alkaline metal.

As to the starting compounds (II), (III), (IV) and (V), some of them are novel and can be prepared by the procedures described in the preparations and Examples mentioned later or a conventional manner.

Throughout the present specification, the amino acid, peptides, protective groups, condensing agents, etc. are indicated by the abbreviations according to the IUPAC-IUB (Commission on Biological Nomenclature) which are in common use in the field of art.

Moreover, unless otherwise indicated, the amino acids and their residues when shown by such abbreviations are meant to be L-configured compounds and residues.

Suitable pharmaceutically acceptable salts of the starting and object compound are conventional non-toxic salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, maleate,

tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4 carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" may include a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, in which the most preferred one is methyl.

Suitable "aryl" and the aryl moiety of "arylamino" may include phenyl, tolyl, xylyl, mesityl, cumenyl, naphtyl, and the like, in which the preferred one is C_6-C_{10} aryl and the most preferred one is phenyl.

Suitable "ar(lower)alkyl" may include mono- or di- or triphenyl(lower)alkyl (e.g. trityl, benzhydryl, benzyl, phenethyl, etc.), and the like.

Suitable "lower alkylene" is one having 1 to 6 carbon atom(s) and may include methylene, ethylene, trimethylene, propylene, tetramethylene, methyltrimethylene, hexamethylene, and the like, in which the preferred one is

methylene, ethylene or trimethylene.

Suitable "lower alkenylene" is one having 2 to 6 carbon atom(s) and may include vinylene, propenylene, and the like, in which the preferred one is vinylene.

Suitable "lower alkylimino "may include methylimino, ethylimino, and the like.

Suitable "an amino acid residue"means a bivalent residue derived from an amino acid, and such amino acid may be glycine (Gly), D- or L- alanine (Ala), β-alanine (βAla), D- or L- valine (Val), D- or L- leucine (Leu), D- or L- isoleucine (Ile), D- or L- serine (Ser), D- or L- threonine (Thr), D- or L- cysteine (Cys), D- or L- methionine (Met), D- or L- phenylalanine (Phe), D- or L-tryptophan (Trp), D- or L- tyrosine (Tyr), D- or L- proline (Pro), D- or L- didehydroproline (ΔPro) such as 3,4-didehydroproline (Δ(3,4)Pro), D- or L- hydroxyproline (Pro(OH)) such as 3-hydroxyproline (Pro(3OH)) and 4-hydroxyproline (Pro(4OH)), D- or L- azetidine-2-carboxylic acid (Azt), D- or L- thioproline (Tpr), D- or L- aminoproline ($Pro(NH_2)$) such as 3-aminoproline ($Pro(3NH_2)$) and 4-aminoproline ($Pro(4NH_2)$), D- or L- pyroglutamic acid (pGlu), D- or L- 2-aminoisobutyric acid (Aib), D- or L- glutamic acid (Glu), D- or L- aspartic acid (Asp), D- or L- glutamine (Gln), D- or L- asparagine (Asn), D- or L- lysine (Lys), D- or L- arginine (Arg), D- or L- histidine (His), D- or L- ornithine (Orn), D- or L- hydroxypiperidinecarboxylic acid such as 5-hydroxypiperidine-2-carboxylic acid, D- or L- mercaptoproline (Pro(SH)) such as 3-mercaptoproline (Pro(3SH)) and 4-mercaptoproline (Pro(4SH)), whose side chains, which are amino, hydroxy, thiol or carboxy groups, may be substituted by the suitable substituent(s). Said suitable substituent(s) may include acyl such as carbamoyl, lower alkanoyl (e.g., formyl, acetyl, etc.), lower alkoxycarbonyl (e.g.,t-butoxycarbonyl, etc.),

trihalo(lower)alkoxycarbonyl (e.g. 2,2,2-trichloroethoxycarbonyl, etc.), ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), lower alkylsulfonyl (e.g., mesyl ethylsulfonyl, etc.), lower alkoxalyl (e.g., methoxyalyl, ethoxyalyl, etc.), arylsulfonyl (e.g., phenylsulfonyl, tolylsulfonyl, etc.), haloar(lower)alkoxycarbonyl (e.g., o-chlorobenzyloxycarbonyl, etc.), carboxy(lower)alkanoyl (e.g., carboxyacetyl, carboxypropionyl, etc.), glycyl, β-alanyl, N-lower alkoxycarbonylglycyl (e.g., N-t-butoxycarbonylglycyl, etc.) and N-lower alkoxycarbonyl-β-alanyl (e.g., N-t-butoxycarbonyl-β-alanyl, etc.), N,N-di(lower)alkylamino(lower)alkanoyl (e.g., N,N-dimethylaminoacetyl, N,N-diethylaminoacetyl, N,N-dimethylaminopropionyl, N,N-diethylaminopropionyl, etc.), carboxyalyl, morpholinocarbonyl, amino(lower)alkanoyl (e.g., aminoacetyl, aminopropionyl, etc.), N-ar(lower)alkoxycarbonylamino(lower)alkanoyl (e.g, N-benzyloxycarbonylaminoacetyl, etc.), threonyl, N-lower alkoxycarbonylthreonyl (e.g. N-t-butoxycarbonylthreonyl, etc.), N-lower alkanoylthreonyl (e.g., N-acetylthreonyl, etc.), N-lower alkoxycarbonyl(lower)alkyl-N-lower alkoxycarbonylamino(lower)alkanoyl (e.g., N-t-butoxycarbonylmethyl-N-t-butoxycarbonylaminoacetyl, etc.), α-glutamyl, N-ar(lower)alkoxycarbonyl-O-ar(lower)-alkyl-α-glutamyl (e.g., N-benzyloxycarbonyl-O-benzyl-α-glutamyl, etc.), γ-glutamyl, N-ar(lower)alkoxycarbonyl-O-ar(lower)alkyl-γ-glutamyl (e.g., N-benzyloxycarbonyl-O-benzyl-γ-glutamyl, etc.), lower alkyl (e.g., methyl, ethyl, t-butyl, etc.), carboxy(lower)alkyl (e.g. carboxymethyl, etc.), protected carboxy (lower) alkyl such as esterified carboxy (lower) alkyl (e.g. ethoxycarbonylmethyl, etc.), morpholino, glycino amide, threonino

amide, N'-glutamino N-lower alkylamide (e.g., N'-glutamino N-t-butylamide, etc.), di(lower)alkylamino (e.g. dimethylamino, etc.), ar(lower)alkyl (e.g., benzyl, phenethyl, etc.), trihalo(lower)alkyl (e.g., 2,2,2-trichloroethyl, etc.), lower alkoxycarbonyl(lower)alkyl (e.g., methoxycarbonylmethyl, ethoxycarbonylmethyl, t-butoxycarbonylmethyl, etc.), or usual protecting group used in the field of art. In case that such amino acid contain a thio, it may be its sulfoxide or sulfone.

Suitable "carboxy(lower)alkyl" may include carboxymethyl, carboxyethyl, carboxypropyl, and the like.

Suitable "protected carboxy(lower)alkyl" means the above-mentioned carboxy(lower)alkyl, in which the carboxy group is protected by a conventional protective group such as esterified carboxy group. Preferred example of the ester moiety thereof may include lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, tert-butyl ester, etc.), and the like.

Suitable "carbamoyl(lower)alkyl which may have suitable substituent(s)" may include carbamoyl(lower)alkyl (e.g., carbamoylmethyl, carbamoylethyl, carbamoylpropyl, etc.), carbamoyl(lower)alkyl having suitable substituent(s) such as lower alkylcarbamoyl(lower)alkyl (e.g., methylcarbamoylmethyl, ethylcarbamoylmethyl, etc.), amino(lower)alkylcarbamoyl(lower)alkyl (e.g., aminomethylcarbamoylmethyl, aminoethylcarbamoylmethyl, etc.), lower alkylamino(lower)alkylcarbamoyl(lower)alkyl (e.g., dimethylaminomethylcarbamoylmethyl, dimethylaminoethylcarbamoylmethyl, etc.), and the like.

Suitable "lower alkyl which may have suitable substituent(s)" may include a conventional group, which is used in the field of art such as lower alkyl, carboxy(lower)alkyl, protected carboxy(lower)alkyl, carbamoyl(lower)alkyl which may have suitable substituent(s), each of which is as exemplified above,

amino(lower)alkyl, protected amino(lower)alkyl, each of which is as exemplified below,
lower alkylamino(lower)alkyl (e.g. dimethylaminomethyl, dimethylaminoethyl, etc.), hydroxy(lower)alkyl (e.g., hydroxymethyl, hydroxyethyl, etc.), protected hydroxy(lower)alkyl such as acyloxy(lower)alkyl (e.g. acetyloxyethyl, etc.) halo(lower)alkyl (e.g. trifluoromethyl, etc.), pyrrolidinyl(lower)alkyl (e.g. pyrrolidin-1-ylethyl, etc.), and the like.

Suitable "an amino acid residue containing an amino, a hydroxy and/or a carboxy" may include a bivalent residue of an amino acid such as Pro(4OH), Ser, Thr, Tyr, and the like.

Suitable "an amino acid residue containing a protected amino, a protected hydroxy and/or a protected carboxy" means the above-mentioned group, in which the amino, hydroxy and/or carboxy is protected by a conventional group used in the field of the art such as carbamoyl, lower alkylsulfonyl (e.g., mesyl, ethylsulfonyl, etc.), arylsulfonyl (e.g., phenylsulfonyl, tolylsulfonyl, etc.), lower alkoxycarbonyl(lower)alkyl (e.g., methoxycarbonylmethyl, ethoxycarbonylmethyl, etc.), and the like.

Suitable "pyridyl(lower)alkyl" may include 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, and the like.

Suitable group of the formula :

, in which R^4 and R^5 are linked together to form benzene-condensed lower alkylene, may include 1-indolinyl, 2-isoindolinyl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, and the like.

Suitable "hydroxy(lower)alkyl" may include hydroxymethyl, hydroxyethyl, hydroxypropyl, and the like.

Suitable "protected hydroxy(lower)alkyl" means the above-mentioned hydroxy(lower)alkyl, in which the hydroxy

group is protected by a conventional protective group such as acyl (e.g. acetyl, etc.), and may include acetyloxyethyl and the like.

Suitable "amino protective group" may be a conventional protective group, which is used in the field of amino acid and peptide chemistry, that is, may include acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, etc.), lower alkanesulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), and the like.

Suitable "carboxy(lower)alkoxy" may include carboxymethyl, carboxyethoxy, carboxypropoxy, and the like.

Suitable "protected carboxy(lower)alkoxy" means the above-mentioned carboxy(lower)alkoxy, in which the carboxy group is protected by a conventional protective group such as esterified carboxy group. Preferred example of the ester moiety thereof may include lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, tert-butyl ester, etc.), and the like.

Suitable "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, hexyloxy, and the like.

Suitable "an amino acid residue containing sulfonyloxy which has a suitable substituent" means a bivalent residue derived from an amino acid containing sulfonyloxy which has a suitable substituent, in which "sulfonyloxy which has a suitable substituent" may include lower alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy, etc.), halo(lower)alkylsulfonyloxy (e.g., trifluoromethylsulfonyloxy, etc.), arylsulfonyloxy

(e.g., phenylsulfonyloxy, tolylsulfonyloxy, etc.), and the like.

Suitable "an amino acid residue containing an azido" may include a bivalent residue of an amino acid such as Pro($4N_3$), and the like.

Suitable "an amino acid residue containing an amino" may include a bivalent residue of an amino acid such as Pro($4NH_2$), and the like.

Suitable "amino (lower) alkyl" may include aminomethyl, aminoethyl, aminopropyl, and the like.

Suitable "protected amino(lower) alkyl "means the above-mentioned amino (lower) alkyl, in which the amino group is protected by a conventional protective group such as acylamino group. Preferred example of the acyl moiety thereof may include lower alkoxycarbonyl (e.g. t-butoxycarbonyl, etc.), and the like.

Suitable "guanidino (lower) alkyl "may include guanidinomethyl, guanidinoethyl, guanidinopropyl, and the like.

Suitable "halogen" may include chloro, fluoro, and the like.

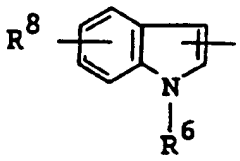
Suitable "alkaline metal "may include sodium, potassium, and the like.

Suitable substituent on R^1 moiety may include a conventional group, which is used in the field of amino acid and peptide chemistry, such as lower alkyl which may have suitable substituent(s), amino protective group, each as defined above, hydroxy, halogen (e.g. fluoro, chloro, etc.), lower alkoxy (e.g. methoxy, butoxy, etc.), N,N-di(lower)alkylamino (e.g. dimethylamino, etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, t-butoxycarbonyl, etc.), lower alkyleneamino(lower)alkyl (e.g. pyrrolidin-1-ylethyl, etc.), and the like.

Suitable substituent on R^3 moiety may include a conventional group, which is used in the field of amino acid and peptide chemistry, such as lower alkyl which may have suitable substituent(s), carboxy(lower)alkoxy, protected carboxy(lower)alkoxy, each as defined above, halogen (e.g. fluoro, chloro, etc.), lower alkoxy (e.g. methoxy, butoxy, etc.), nitro, amino, protected amino, in which amino protective group is as defined above, and the like.

The preferred embodiments of R^1, R^2, R^3, R^4, R^5, A and Y are as follows.

R^1 is di(lower) alkoxyphenyl, mono-or di-or triphenyl-(lower) alkyl which may have lower alkoxy, indolinyl, pyridyl, or a group of the formula :



wherein R^6 is lower alkyl, di(lower)alkylamino-(lower)alkyl, pyrrolidinyl(lower)alkyl, carboxy(lower)alkyl, esterified carboxy(lower)alkyl, amino(lower) alkyl, guanidino(lower)alkyl, pyridyl(lower)-alkyl or acylamino(lower)alkyl, and

R^8 is hydrogen or halogen,

R^2 is hydrogen or lower alkyl,

R^3 is lower alkyl or halogen,

R^4 is lower alkyl, carboxy(lower)alkyl or esterified carboxy(lower)alkyl,

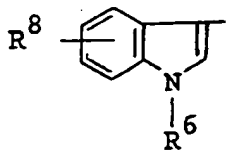
R^5 is mono-or di-or triphenyl(lower)alkyl or pyridyl(lower)-alkyl,

A is a bivalent residue derived from an amino acid which may have suitable substituent such as hydroxyproline, glycine, serine, methionine, lysine, histidine, glutamine, thioproline and aminoproline, whose side chains may be substituted by the substituent selected from the group consisting of lower alkoxycarbonyl, carboxy(lower)alkyl, esterified carboxy(lower)alkyl and lower alkylsulfonyl, and

Y is bond, lower alkylene, lower alkenylene or lower alkylimino.

Particularly, the preferred embodiments of R^1, R^2, R^3, R^4, R^5, A and Y are as follows.

R^1 is a group of the formula :



wherein R^6 is lower alkyl, and

R^8 is hydrogen,

R^2 is hydrogen;

R^3 is lower alkyl or halogen,

R^4 is lower alkyl,

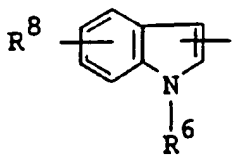
R^5 is phenyl(lower)alkyl,

A is hydroxyproline, and

Y is bond.

Also, the preferred embodiments of R^1, R^2, R^3, R^4, R^5, A and Y are as follows.

R^1 is di(lower)alkoxyphenyl, mono-or di-or triphemyl(lower)-alkyl which may have lower alkoxy, indolinyl, pyridyl, or a group of the formula :



wherein R^6 is lower alkyl, di(lower)alkylamino-(lower)alkyl, pyrrolidinyl(lower)alkyl, carboxy(lower)alkyl, esterified carboxy-(lower)alkyl, amino(lower) alkyl, guanidino(lower)alkyl, pyridyl(lower)alkyl or acylamino(lower)alkyl, and

R^8 is hydrogen or halogen,

R^2 is hydrogen or lower alkyl,

R^3 is hydrogen,

R^4 is lower alkyl, carboxy(lower)alkyl or esterified carboxy(lower)alkyl.

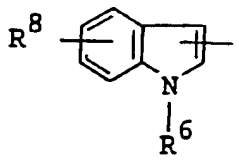
R^5 is mono-or di-or triphenyl(lower)alkyl,

A is a bivalent residue derived from an amino acid excepting hydroxyproline which may have suitable substituent such as glycine, serine, methionine, lysine, histidine, glutamine, thioproline and aminoproline, whose side chains may be substituted by the substituent selected from the group consisting of lower alkoxycarbonyl, carboxy(lower)alkyl, esterified carboxy(lower)alkyl and lower alkylsulfonyl, and

Y is bond, lower alkylene, lower alkenylene or lower alkylimino.

Also, the preferred embodiments of R^1, R^2, R^3, R^4, R^5, A and Y are as follows.

R^1 is di(lower)alkoxyphenyl, mono-or di-or triphemyl(lower)-alkyl which may have lower alkoxy, indolinyl, pyridyl, or a group of the formula :



wherein R^6 is di(lower)alkylamino(lower)alkyl, pyrrolidinyl(lower)alkyl, carboxy(lower)alkyl, esterified carboxy(lower)alkyl, amino(lower)-alkyl, guanidino(lower)alkyl, pyridyl(lower)-alkyl or acylamino(lower)alkyl, and

R^8 is hydrogen or halogen,

R^2 is hydrogen or lower alkyl,

R^3 is hydrogen,

R^4 is lower alkyl, carboxy(lower)alkyl or esterified carboxy(lower)alkyl.

R^5 is mono-or di-or triphenyl(lower)alkyl,

A is a bivalent residue derived from hydroxyproline which may be substituted by the substituent selected from the group consisting of carboxy(lower)alkyl, esterified carboxy(lower)alkyl and lower alkylsulfonyl, and

Y is bond, lower alkylene, lower alkenylene or lower alkylimino.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the amino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsyliy acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (II) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

Suitable reactive derivative at the carboxy group of the compound (III) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride within acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous

acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

Suitable salts of the compound (III) and its reactive derivative may be a base salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], or the like, and an acid addition salt as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform,

methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphoniumhexafluorophosphate; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine,

or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

The object compound (I) or a salt thereof can be prepared by reacting the compound (IV) or its reactive derivative at the amino group or a salt thereof with the compound (V) or its reactive derivative at the carboxy group or a salt thereof.

Suitable salts of the compound (IV) and its reactive derivative can be referred to the ones as exemplified for the compound (II).

Suitable salts of the compound (V) and its reactive derivative can be referred to the ones as exemplified for the compound (III).

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. reactive derivatives, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 3

The object compound (I-b) or a salt thereof can be prepared by subjecting the compound (I-a) or a salt thereof to elimination reaction of the amino, hydroxy and/or carboxy protective group.

In the present elimination reaction, all conventional methods used in the elimination reaction of the carboxy protective group, for example, hydrolysis, reduction, elimination using Lewis acid, etc. are applicable. When the carboxy protective group is an ester, it can be eliminated by hydrolysis or elimination using Lewis acid. The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-one, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[5.4.0]undecene-5 or the like. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

The present hydrolysis is usually carried out in an organic solvent, water, or a mixed solvent thereof.

The reaction temperature is not critical, and it may suitably be selected in accordance with the kind of the carboxyprotective group and the elimination method.

The elimination using Lewis acid is carried out by reacting the compound (I-a) or a salt thereof with Lewis acid such as boron trihalide (e.g. boron trichloride, boron trifluoride, etc.), titanium tetrahalide (e.g.

titanium tetrachloride, titanium tetrabromide, etc.), tin tetrahalide (e.g. tin tetrachloride, tin tetrabromide, etc.), aluminum halide (e.g. aluminum chloride, aluminum bromide, etc.), trihaloacetic acid (e.g. trichloroacetic acid, trifluoroacetic acid, etc.) or the like. This elimination reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.) and is usually carried out in a solvent such as nitroalkane (e.g. nitromethane, nitroethane, etc.), alkylene halide (e.g. methylene chloride, ethylene chloride, etc.), diethyl ether, carbon disulfide or any other solvent which does not adversely affect the reaction. These solvents may be used as a mixture thereof.

The reduction elimination can be applied preferably for elimination of the protective group such as halo(lower)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl, etc.) ester, ar(lower)alkyl (e.g. benzyl, etc.) ester or the like.

The reduction method applicable for the elimination reacting may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a salt of chromium compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or an inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, etc.); and conventional catalytic reduction in the presence of a conventional metallic catalyst (e.g. palladium carbon, Raney nickel, etc.).

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming.

Process 4

The object compound (I-d) or a salt thereof can be prepared by subjecting the compound (I-c) or a salt

thereof to elimination reaction of the carboxy or amino, protective group.

This reaction can be carried out in substantially the same manner as Process 3, and therefore the reaction mode and reaction conditions [e.g. bases, acids, reducing agents, catalysts, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 3.

Process 5

The object compound (I-a) or a salt thereof can be prepared by subjecting the compound (I-b) or its reactive derivative at the amino, hydroxy and/or carboxy group or a salt thereof to introduction reaction of the amino, hydroxy and/or carboxy protective group.

The reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

The present reaction includes, within its scope, the case that the amino group on R^1 is reacted during the reaction or at the post-treating step of the present process.

Process 6-(i)

The compound (I-f) or a salt thereof can be prepared by reacting the compound (I-e) or a salt thereof with the compound (VI).

The reaction is usually carried out in a conventional solvent such as dimethyl sulfoxide or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

Process 6-(ii)

The object compound (I-g) or a salt thereof can be prepared by subjecting the compound (I-f) or a salt thereof to hydrogenation. This reaction is usually carried out in the presence of triphenylphosphine, palladium on carbon, or the like.

The reaction is usually carried out in a conventional solvent such as alcohol (e.g., methanol, ethanol, etc.), or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 7

The object compound (I-j) or a salt thereof can be prepared by subjecting the compound (I-h) or a salt thereof to elimination reaction of the carboxy protective group.

This reaction can be carried out in substantially the same manner as Process 3, and therefore the reaction mode and reaction conditions [e.g. bases, acids, reducing agents, catalysts, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 3.

Process 8

The object compound (I-k) or a salt thereof can be prepared by subjecting the compound (I-f) or a salt thereof to introduction reaction of amidino group.

This reaction is usually carried out in the presence of introducing agent of amidino group such as 3,5-dimethylpyrazole-1-carboxamidine, and the like, and in the presence of a base such as trialkylamino (e.g. triethylamine, etc.).

The reaction temperature is not critical and the

reaction is usually carried out under cooling to heating.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

The object compounds (I) and pharmaceutically acceptable salt thereof have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin A antagonism or neurokinin B antagonism, and therefore are useful for treating or preventing tachykinin mediated diseases, particularly substance P mediated diseases, for example, respiratory diseases such as asthma, bronchitis rhinitis, cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like; pains or aches (e.g. migraine, headache, toothache, cancerous pain, back pain, etc.); and the like.

Further, it is expected that the object compounds (I) of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, uveitis, and the like; gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like; inflammatory diseases such as nephritis, and the like; circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, and the like; epilepsy; spastic paralysis;

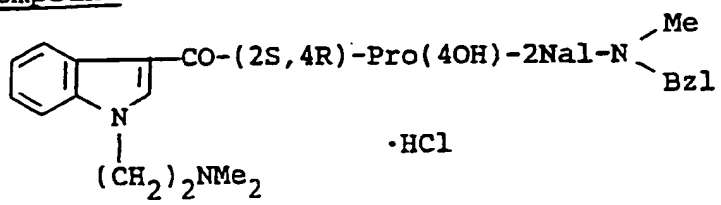
pollakiuria; dementia; Alzheimer's diseases; schizophrenia; Huntington's chorea; carcinoid syndrome; and the like, and useful for immunosuppresive agent.

For therapeutic purpose, the compounds (I) and pharmaceutically acceptable salts thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension, emulsion, or the like. If desired, there may be included in these preparation, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compounds (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of some representative compound of the compound (I) is shown in the following.

Test Compound :

(a) 

(1) ^{3}H-Substance P receptor binding

Test Method :

(a) Crude lung membrane preparation

Male Hartly strain guinea pigs were sacrificed by decapitation. The trachea and lung were removed and homogenized in buffer (0.25 M sucrose, 50 mM Tris-HCl pH 7.5, 0.1 mM EDTA) by suing Polytoron (Kinematica). The homogenate was centrifuged (1000 xg, 10 min) to remove tissue clumps and the supernatant was centrifuges (14000 xg 20 min) to yield pellets. The pellets were resuspended in buffer (5 mM Tris-HCl pH 7.5), homogenized with a teflon homogenizer and centrifuged (14000 xg, 20 min) to yield pellets which were referred to as crude membrane fractions. The obtained pallets were stored at -70°C until use.

(b) ^{3}H-Substance P binding to preparation membrane

Frozen crude membrane fractions were thawed and resuspended in Medium 1 (50 mM Tris-HCl pH 7.5, 5 mM $MnCl_2$, 0.02% BSA, 2 µg/ml chymostatin, 4µg/ml leupeptin, 40 µg/ml bacitracin.) ^{3}H-substance P (1 nM) was incubated with 100 µl of the membrane preparation in Medium 1 at 4°C for 30 minutes in a final volume of 500 µl. At the end of the incubation period, reaction mixture was quickly filtered over a Whatman GF/B glass filter (pretreated with 0.1% polyethylene imine for 3 hours prior to use) under aspiration. The filters were then washed four times with 5 ml of the buffer (50 mM Tris-HCl, pH 7.5). The radioactivity was counted in 5 ml of Aquazol-2 in Packerd scintillation counter (Packerd TRI -CARB 4530).

Test Result :

Test Compound (0.g µg/ml)	Inhibition (%)
(a)	100

The following examples are given for purpose of

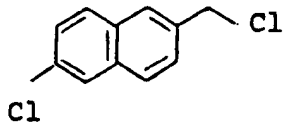
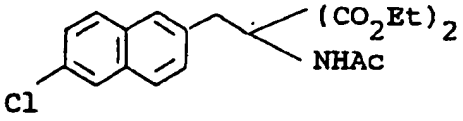
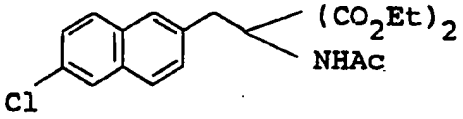
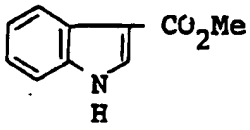
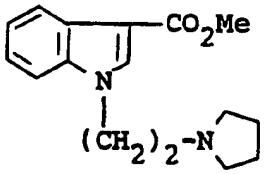
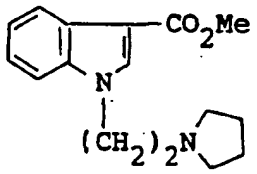
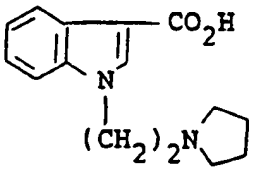
illustrating the present invention in detail.

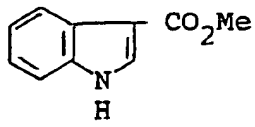
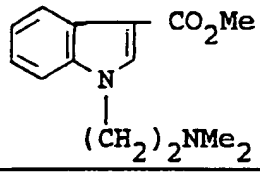
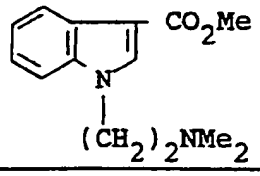
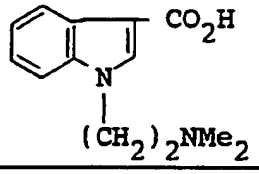
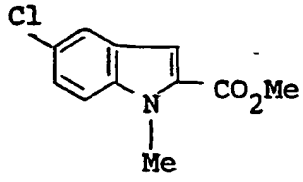
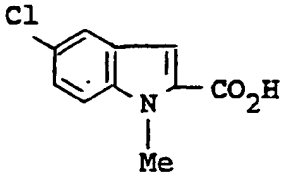
In these examples, there are employed the following abbreviations in addition to the abbreviations adopted by the IUPAC-IUB.

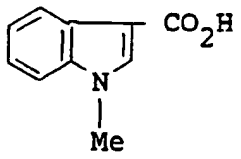
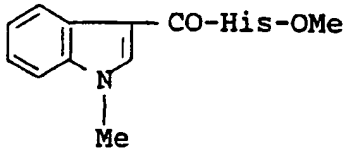
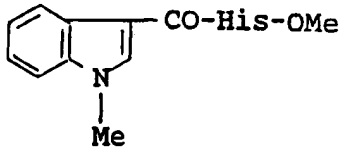
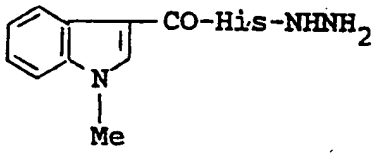
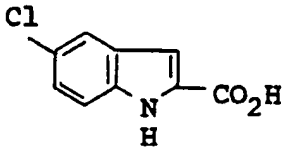
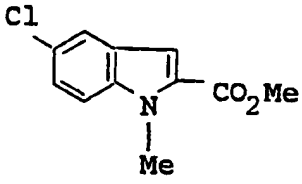
Ac	:	acetyl
Boc	:	t-butoxycarbonyl
Bu^t	:	t-butyl
Bzh	:	Benzhydryl
Bzl	:	benzyl
DMF	:	dimethylformamide
DMSO	:	dimethylsulfoxide
Et	:	ethyl
HOBT	:	N-hydroxybenzotriazole
IPE	:	isopropyl ether
Me	:	methyl
2Nal	:	3-(2-naphthyl)alanine
2Nal(6-Cl)	:	3-[2-(6-chloronaphthyl)]alanine
2Nal(6-Me)	:	3-[2-(6-methylnaphthyl)]alanine
HCl/DOX	:	hydrogen chloride in 1,4-dioxane
Pro(4OH)	:	4-hydroxyproline
TEA	:	triethylamine
TFA	:	trifluoroacetic acid
THF	:	tetrahydrofuran
Tpr	:	thioproline
WSC	:	1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide
Z	:	benzyloxycarbonyl

The Starting Compounds used and the Object Compounds obtained in the following examples are given in The Table as below, in which the formulae of the former compounds are in the upper and the formulae of the latter compounds are in the lower, respectively.

Table

Preparation No.	Formula
1	
	
2	
	Ac-2Nal(6-Cl)-OH
3	Ac-2Nal(6-Cl)-OH
	H-2Nal(6-Cl)-OH
4	
	
5	
	

Preparation No.	Formula
6	
	
7 - (1)	
	
7 - (2)	
	
8	H-2Nal(6-Cl)-OH
	Boc-2Nal(6-Cl)-OH
9	H-2Nal(6-Me)-OH
	Boc-2Nal(6-Me)-OH

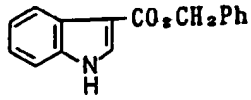
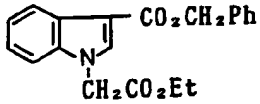
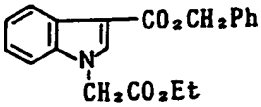
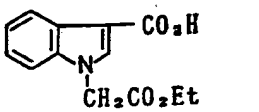
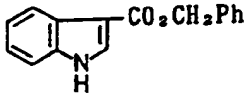
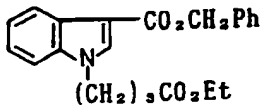
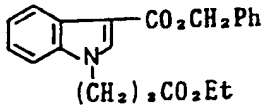
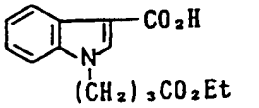
Preparation No.	Formula
10	
	
11	
	
12	
	
13	Boc-2Nal(6-Cl)-OH
	Boc-2Nal(6-Cl)-N(Me)(Bzl)
14	Boc-2Nal(6-Me)-OH
	Boc-2Nal(6-Me)-N(Me)(Bzl)

Preparation No.	Formula
15	Boc-2Nal(6-Cl)-N(Me)(Bzl)
	HCl·H-2Nal(6-Cl)-N(Me)(Bzl)
16	Boc-2Nal(6-Me)-N(Me)(Bzl)
	HCl·H-2Nal(6-Me)-N(Me)(Bzl)
17	HCl·H-2Nal(6-Cl)-N(Me)(Bzl)
	Boc-(2S,4R)-Pro(4OH)-2Nal(6-Cl)-N(Me)(Bzl)
18 - (1)	HCl·H-2Nal(6-Me)-N(Me)(Bzl)
	Boc-(2S,4R)-Pro(4OH)-2Nal(6-Me)-N(Me)(Bzl)
18 - (2)	HCl·H-2Nal-N(Me)(Bzl)
	Boc-Gly-2Nal-N(Me)(Bzl)
18 - (3)	HCl·H-2Nal-N(Me)(Bzl)
	Boc-Gln-2Nal-N(Me)(Bzl)

Preparation No.	Formula
18 - (4)	HCl·H-2Nal-N(Me)(Bzl)
	Boc-Ser-2Nal-N(Me)(Bzl)
18 - (5)	HCl·H-2Nal-N(Me)(Bzl)
	Boc-Met-2Nal-N(Me)(Bzl)
18 - (6)	HCl·H-2Nal-N(Me)(Bzl)
	Boc-Tpr-2Nal-N(Me)(Bzl)
18 - (7)	HCl·H-2Nal-N(Me)(Bzl)
	Z-Lys(Boc)-2Nal-N(Me)(Bzl)
18 - (8)	HCl·H-2Nal-N(Me)(Bzl)
	Boc-D-Met-2Nal-N(Me)(Bzl)
19	Boc-(2S,4R)-Pro(4OH)-2Nal(6-Cl)-N(Me)(Bzl)
	HCl·H-(2S,4R)-Pro(4OH)-2Nal(6-Cl)-N(Me)(Bzl)

Preparation No.	Formula
20 - (1)	Boc-(2S,4R)-Pro(4OH)-2Nal(6-Me)-N(Me)(Bzl)
	HCl·H-(2S,4R)-Pro(4OH)-2Nal(6-Me)-N(Me)(Bzl)
20 - (2)	Boc-Gly-2Nal-N(Me)(Bzl)
	HCl·H-Gly-2Nal-N(Me)(Bzl)
20 - (3)	Boc-Gln-2Nal-N(Me)(Bzl)
	HCl·H-Gln-2Nal-N(Me)(Bzl)
20 - (4)	Boc-Ser-2Nal-N(Me)(Bzl)
	HCl·H-Ser-2Nal-N(Me)(Bzl)
20 - (5)	Boc-Met-2Nal-N(Me)(Bzl)
	HCl·H-Met-2Nal-N(Me)(Bzl)
20 - (6)	Boc-Tpr-2Nal-N(Me)(Bzl)
	HCl·H-Tpr-2Nal-N(Me)(Bzl)

Preparation No.	Formula
21	Boc-D-Met-2Nal-N(Me)(Bzl)
	HCl·H-D-Met-2Nal-N(Me)(Bzl)
22	Z-Lys(Boc)-2Nal-N(Me)(Bzl)
	H-Lys(Boc)-2Nal-N(Me)(Bzl)
23	Boc-2Nal-OH
	Boc-Me 2Nal-OH
24	Boc-Me2Nal-OH
	Boc-Me2Nal-N(Me)(Bzl)
25	Boc-(2S,4R)-Pro(4OH)-Me2Nal-N(Me)(Bzl)
	H-(2S,4R)-Pro(4OH)-Me2Nal-N(Me)(Bzl)
26	Boc-Me2Nal-N(Me)(Bzl)
	HCl·H-Me2Nal-N(Me)(Bzl)

Preparation No.	Formula
27	HCl·H-Me2Nal-N(Me)(Bzl)
	Boc-(2S,4R)-Pro(4OH)-Me2Nal-N(Me)(Bzl)
28	
	
29	
	
30	
	
31	
	

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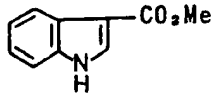
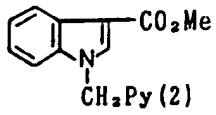
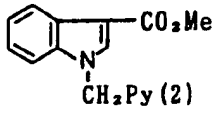
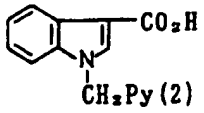
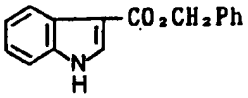
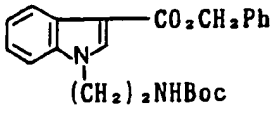
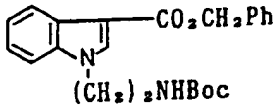
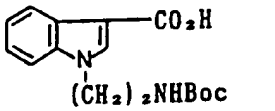
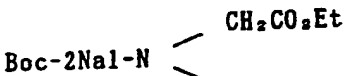
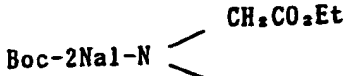
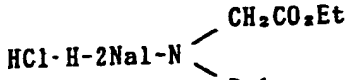
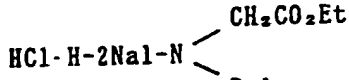
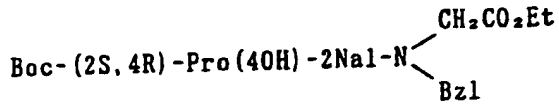
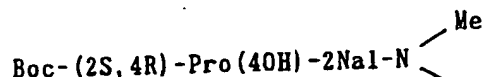
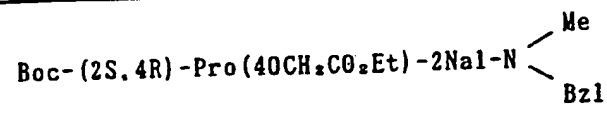
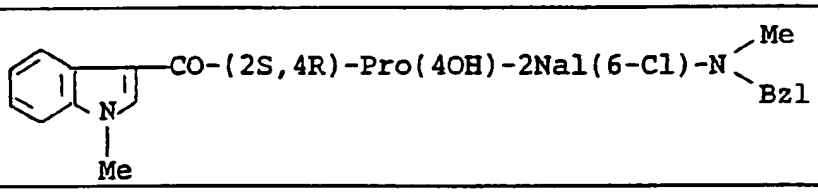
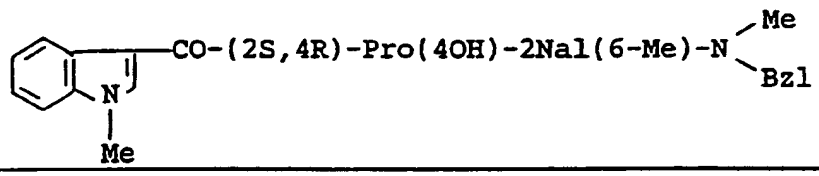
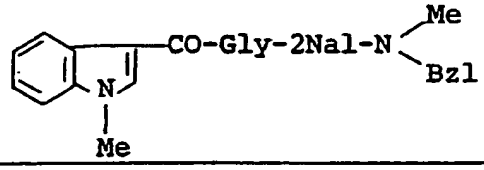
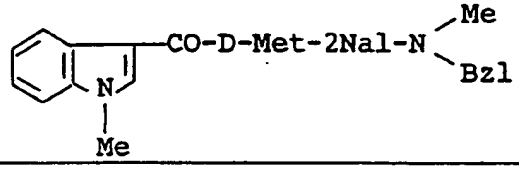
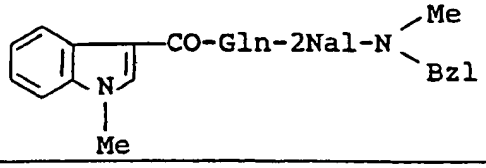
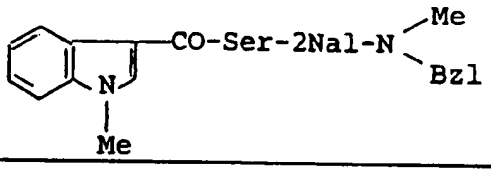
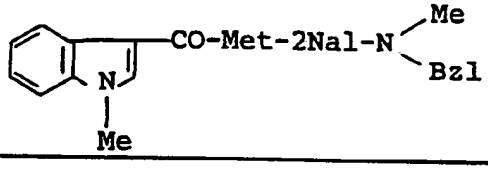
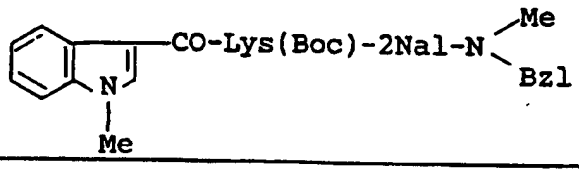
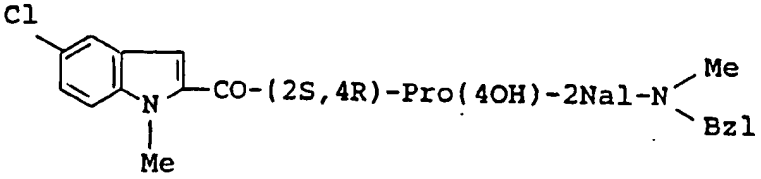
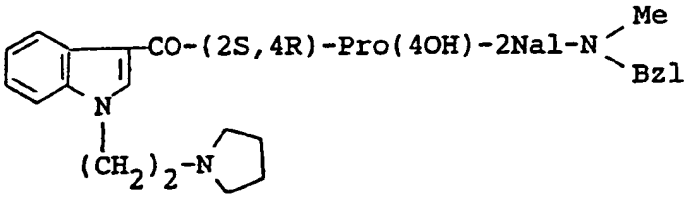
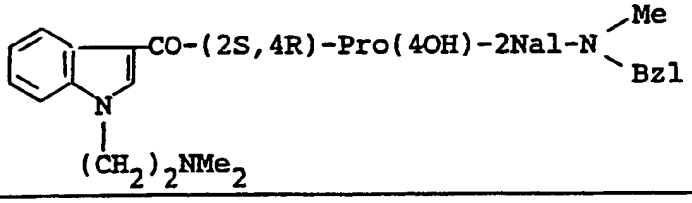
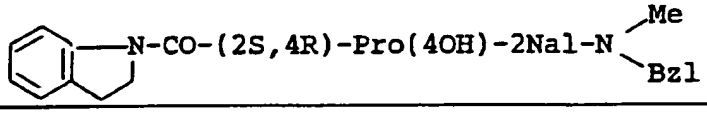
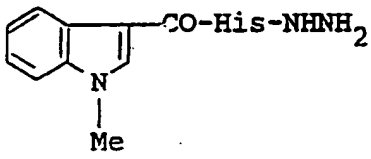
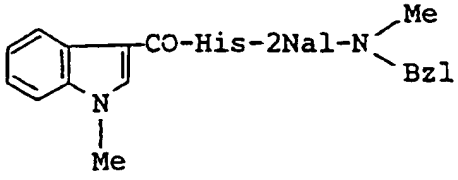
32	
	
33	
	
34	$H_2N(CH_2)_2OH$
	$Bu^tOCONH(CH_2)_2OH$
35	$Bu^tOCONH(CH_2)_2OH$
	$Bu^tOCONH(CH_2)_2OSO_2Me$
36	
	

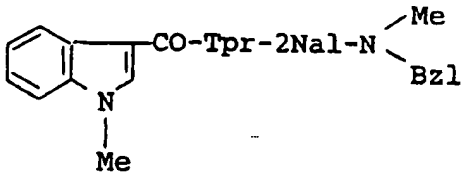
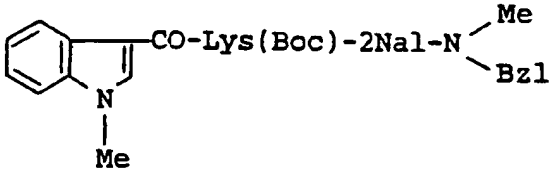
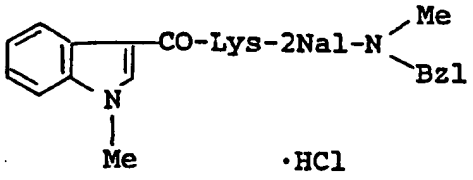
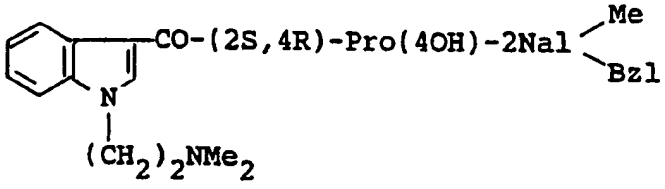
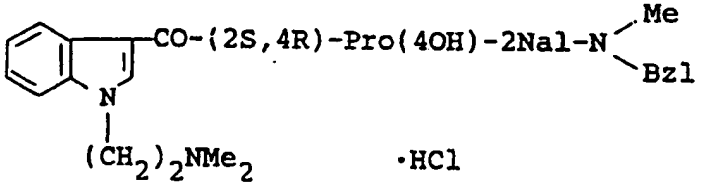
Preparation No.	Formula
37	
	
38	Boc-2Nal-OH
	
39	
	
40	
	
41	
	

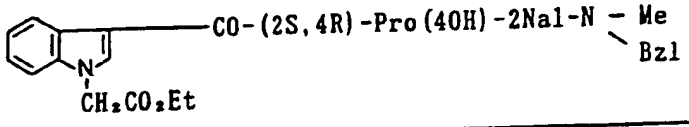
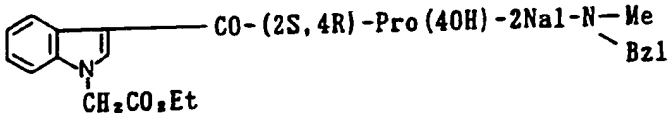
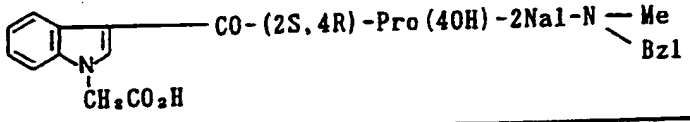
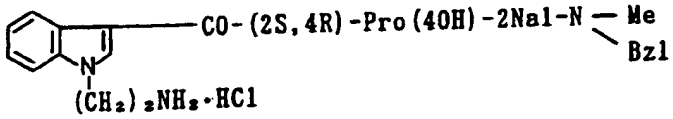
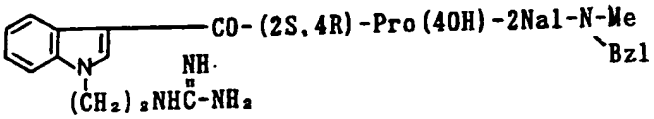
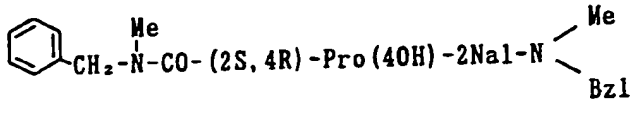
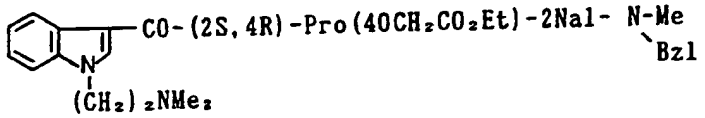
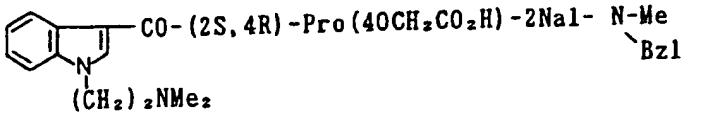
Preparation No.	Formula
42-(1)	Boc-(2S,4R)-Pro(4OH)-2Nal-N(CH$_2$CO$_2$Et)(Bzl)
	HCl·H-(2S,4R)-Pro(4OH)-2Nal-N(CH$_2$CO$_2$Et)(Bzl)
42-(2)	Boc-(2S,4R)-Pro(4OCH$_2$CO$_2$Et)-2Nal-N(Me)(Bzl)
	HCl·H-(2S,4R)-Pro(4OCH$_2$CO$_2$Et)-2Nal-N(Me)(Bzl)

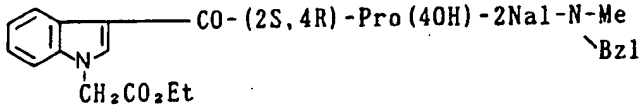
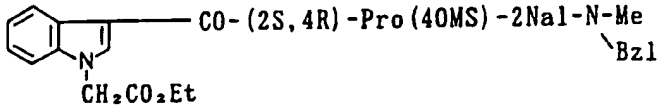
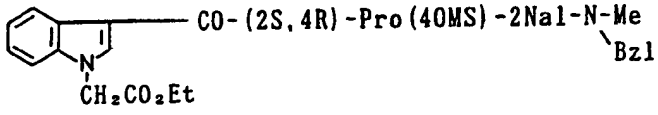
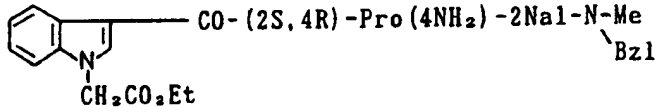
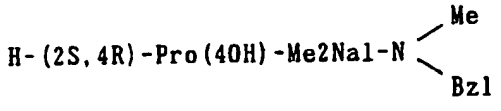
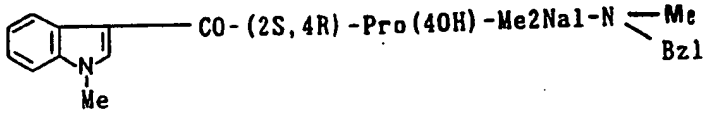
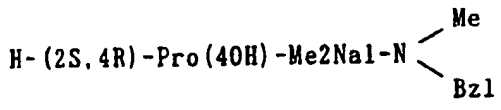
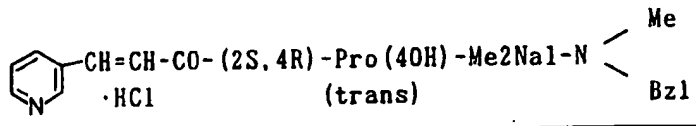
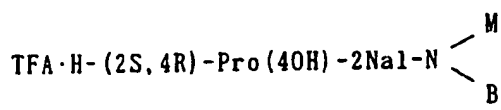
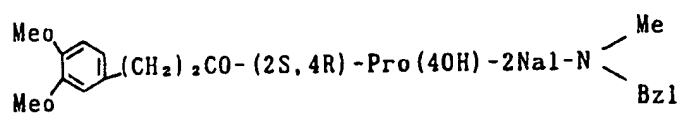
Example No.	Formula
1	HCl·H-(2S,4R)-Pro(4OH)-2Nal(6-Cl)-N(Me)(Bzl)
	
2-(1)	HCl·H-(2S,4R)-Pro(4OH)-2Nal(6-Me)-N(Me)(Bzl)
	
2-(2)	HCl·H-Gly-2Nal-N(Me)(Bzl)
	
2-(3)	HCl·H-D-Met-2Nal-N(Me)(Bzl)
	
2-(4)	HCl·H-Gln-2Nal-N(Me)(Bzl)
	

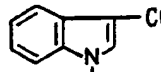
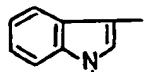
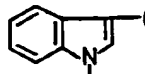
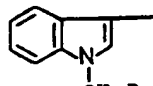
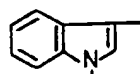
Example No.	Formula
2-(5)	HCl·H-Ser-2Nal-N(Me)(Bzl)
	
2-(6)	HCl·H-Met-2Nal-N(Me)(Bzl)
	
2-(7)	H-Lys(Boc)-2Nal-N(Me)(Bzl)
	
3	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)
	Bzh-CO-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)
4-(1)	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)
	

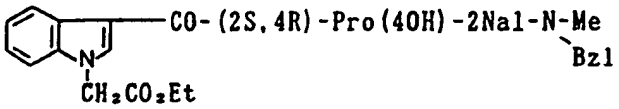
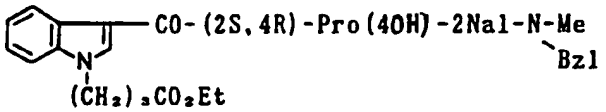
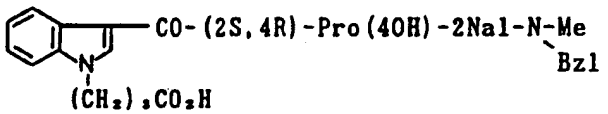
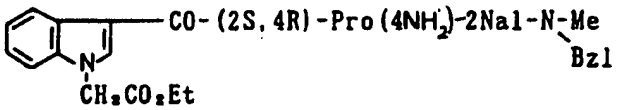
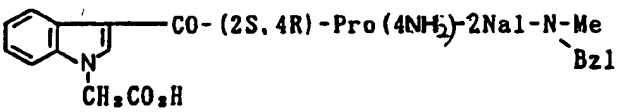
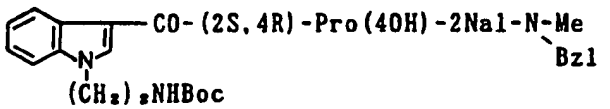
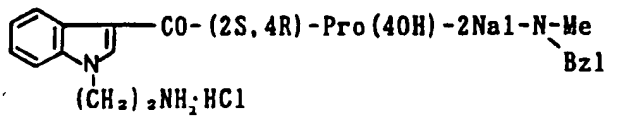
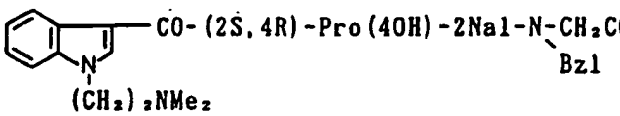
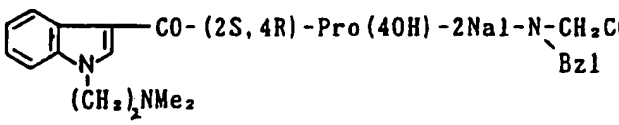
Example No.	Formula
4-(2)	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)Bzl
	
4-(3)	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)Bzl
	
5	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)Bzl
	
6	I 
	II HCl·H-2Nal-N(Me)Bzl
	

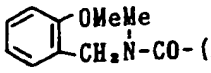
Example No.	Formula
7	HCl·H-Tpr-2Nal-N(Me)(Bzl)
	
8	
	
9	
	

Example No.	Formula
10	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)
	
11	
	
12	
	
13	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)
	
14	
	

Example No.	Formula
15	
	
16	
	
17-(1)	
	
17-(2)	
	
17-(3)	
	

Example No.	Formula
17-(4)	HCl·H-(2S,4R)-Pro(4OH)-2Nal-N(CH$_2$CO$_2$Et)(Bzl)
	 CO-(2S,4R)-Pro(4OH)-2Nal-N(CH$_2$CO$_2$Et)(Bzl) 
17-(5)	HCl·H-(2S,4R)-Pro(4OCH$_2$CO$_2$Et)-2Nal-N(Me)(Bzl)
	 CO-(2S,4R)-Pro(4OCH$_2$CO$_2$Et)-2Nal-N(Me)(Bzl) 
18-(1)	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)
	 CO-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) 
18-(2)	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)
	 CO-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) 
18-(3)	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)
	 CO-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) 

Example No.	Formula
18-(4)	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)
	
19-(1)	
	
19-(2)	
	
20	
	
21	
	

Example No.	Formula
22	TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)
	 OMeMe CH₂N-CO-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl)

Preparation 1

To a solution of sodium ethoxide (6.03 g) in ethanol (340 ml) were added diethyl 2-acetamidomalonate (17.5 g) and Starting Compound (17 g) at room temperature. The mixture was heated under reflux for two and half hours. After cooling, the mixture was filtered and the filtrate was concentrated under vacuum. The resulting crystalline solid was collected by filtration and washed with ethanol and dried to give Object Compound (17.1 g).

mp : 139-141°C

IR (Nujol) : 3380, 1750, 1640, 1510, 1310, 1295, 1210, 1190 cm^{-1}

NMR (DMSO-d_6, δ) : 1.18 (6H, t, J=7.06Hz), 1.98 (3H, s), 3.60 (2H, s), 4.17 (4H, q, J=7.03Hz), 7.15-8.35 (7H, m)

MASS : M^{+1} 391

Preparation 2

To a suspended mixture of Starting Compound (16.9 g) in a mixed solvent of ethanol (170 ml) and water (170 ml) was added potassium hydroxide (1.45 g) and the solution was heated under reflux. Two additional portions of potassium hydroxide (1.45 g each) were added after reflux was begun; once after three hours of reflux and again after two more additional hours of reflux. The total reflux time was seven hours. After cooling, the solution was acidified to pH 1 with concentrated hydrochloric acid and was stirred half an hour under ice-cooling. The precipitates were collected, by filtration, washed with water, and dried to give Object Compound (11.89 g).

IR (Nujol) : 3600, 3520, 3300, 1730, 1620, 1570, 1220, 1185 cm^{-1}

NMR (DMSO-d_6, δ) : 1.77 (3H, s), 3.00 (1H, dd, J=13.7Hz and 9.4Hz), 3.21 (1H, dd, J=13.8Hz and 5.1Hz), 4.45-4.60 (1H, m), 7.45-8.0 (6H, m),

8.26 (1H, d, J=8.1Hz), 12.74 (1H, br s)
MASS : M^{+1} 291

Preparation 3

To a suspended mixture of Starting Compound (8.8 g) in water (176 ml) was added 1N sodium hydroxide solution (31 ml). The solution was warmed to 37°C and the pH was adjusted to 7.5 by an addition of 1N hydrochloric acid. Then cobalt(II) chloride hexahydrate (44 mg) and acylase (trademark : Acylase Amano 15000) (440 mg) were added to the solution. The reaction mixture was stirred at 37°C overnight during which period the pH was maintained at 7.5 by an addition of 1N sodium hydroxide solution. The precipitates were collected by filtration, washed with water, and dried to give Object Compound (3.6 g).

IR (Nujol) : 2600-2450, 1615, 1555, 1530, 1420, 1310 cm^{-1}
MASS : M^{+1} 249
$[\alpha]_D$: -11.56 (C=0.5, 1N NaOH)

Preparation 4

To an ice-cooled solution of Starting Compound (3.0 g) in methylene chloride (60 ml) were added cetyltrimethylammonium chloride (0.55 g), powdered sodium hydroxide (3.42 g), and 1-(2-chloroethyl)pyrrolidine hydrochloride (2.94 g). The mixture was stirred at room temperature overnight. After filtration, the filtrate was washed with sodium chloride solution and was dried with magnesium sulfate. The crude product was purified on a silica gel column (105 g) eluting with chloroform-methanol (from 50:1 to 30:1) to give Object Compound (2.90 g) as an oil.

IR ($CHCl_3$) : 1700 cm^{-1}
NMR (DMSO-d_6, δ) : 1.65 (4H, m), 2.50 (4H, m), 2.81 (2H, t, J=6.4Hz), 3.81 (3H, s), 4.36 (2H, t,

J=6.4Hz), 7.17-7.3 (2H, m), 7.60 (1H, m), 8.0 (1H, m), 8.16 (1H, s)

Preparation 5

Starting Compound (2.9 g) was dissolved in a mixture of methanol (58 ml) and 1N sodium hydroxide (22 ml) solution. The mixture was heated under reflux for four hours. After cooling, the mixture was concentrated and ethyl acetate and water were added, and the aqueous layer was separated. The pH was adjusted to 4 with 1N hydrochloric acid and concentrated to dryness under vacuum to give Object Compound. This product was used for the next step without further purification.

NMR (DMSO-d_6, δ) : 1.65 (4H, m), 2.50 (4H, m), 2.81 (2H, t, J=6Hz), 4.34 (2H, t, J=6.5Hz), 7.1-7.25 (2H, m), 7.55 (1H, m), 8.0 (2H, m)

MASS : M^+ 258

Preparation 6

The object compound was obtained according to a similar manner to that of Preparation 4.

IR (Film) : 1700 cm^{-1}

NMR (DMSO-d_6, δ) : 2.17 (6H, s), 2.62 (2H, t, J=6Hz), 3.80 (3H, s), 4.33 (2H, t, J=6Hz), 7.2-7.3 (2H, m), 7.6 (1H, m), 8.0 (1H, m), 8.15 (1H, s)

Preparation 7

The object compounds were obtained according to a similar manner to that of Preparation 5.

(1) mp : 229°C~ (dec.)

IR (Nujol) : 2700, 1695, 1665 cm^{-1}

NMR (DMSO-d_6, δ) : 2.79 (6H, s), 3.50 (2H, t, J=6Hz), 4.75 (2H, t, J=6Hz), 7.20-7.35 (2H, m),

7.77 (1H, m), 8.04 (1H, m), 8.18 (1H, s)

(2) mp : 212°C~
IR (Nujol) : 3450, 2610, 1681, 1520, 880, 850, 815, 795, 760, 732 cm^{-1}
NMR (DMSO-d_6, δ) : 3.38 (1H, br s), 4.02 (3H, s), 7.15-7.80 (4H, m)

Preparation 8

To a suspended mixture of Starting Compound (2.0 g) in a mixed solvent of water (20 ml) and acetone (20 ml) was added TEA (2.46 ml) under ice-cooling. To the solution was added a solution of di-tert-butyldicarbonate (2.1 g) in acetone (5 ml), and the solution was stirred at the same temperature for two hours and at room temperature for additional two hours, during which period, triethylamine (1.23 ml) was added. After removal of the acetone, water (50 ml) was added and the aqueous solution was washed once with diethyl ether. The aqueous layer was then acidified to pH 1 with an addition of 1N hydrochloric acid and was extracted with ethyl acetate. The extract was washed with an aqueous sodium chloride solution and was dried over magnesium sulfate. After evaporation, the crystalline solid was collected and dried to give Object Compound (2.66 g).

mp : 146-148°C
IR (Nujol) : 3370, 1720, 1695, 1520, 1270, 1170 cm^{-1}
NMR (DMSO-d_6, δ) : 1.28 (9H, s), 2.96 (1H, dd, J=23.8Hz and 10.2Hz), 3.20 (1H, dd, J=13.6Hz and 4.5Hz), 4.15-4.3 (1H, s), 7.19 (1H, d, J=8.4Hz), 7.45-7.55 (2H, m), 7.75-8.05 (4H, m), 12.65 (1H, br s)
MASS : M^{+1} 349

Preparation 9

The object compound was obtained according to a

similar manner to that of Preparation 8.

mp : 122°C (dec.)

IR (Nujol) : 3380, 1720, 1690, 1520, 1270, 1180 cm^{-1}

NMR (DMSO-d_6, δ) : 1.29 (9H, s), 2.45 (3H, s), 2.97 (1H, dd, J=23.9Hz and 10.2Hz), 3.17 (1H, dd, J=18.4Hz and 4.6Hz), 4.1-4.3 (1H, m), 7.1-7.8 (7H, m), 12.64 (1H, br s)

MASS : M^{+1} 329

Preparation 10

To a solution of Starting Compound (2.0 g), histidine methyl ester dihydrochloride (2.76 g), and HOBT (1.54 g) in DMF (40 ml) was added WSC (2.08 ml) under ice-cooling. The solution was stirred at the same temperature for an hour and at room temperature overnight. After evaporation, water and ether were added to the residue. The aqueous layer was separated and left standing. The resulting crystalline product was collected, washed, and dried to give Object Compound (2.06 g).

IR (Nujol) : 3180, 1745, 1635, 1545, 1400 cm^{-1}

NMR (DMSO-d_6, δ) : 3.07 (2H, d, J=7.12Hz), 3.62 (3H, s), 3.84 (3H, s), 4.73 (1H, dd, J=13.9Hz and 7.41Hz), 6.95-8.30 (9H, m),

MASS : M^{+1} 326

Preparation 11

To a solution of Starting Compound (2.0 g) in methanol (40 ml) was added hydrazine hydrate (1.79 ml). The solution was stirred at room temperature overnight. The precipitates were collected, washed with methanol, and dried to give Object Compound (1.08 g).

mp : 261°C~ (dec.)

IR (Nujol) : 3400, 3300, 1660, 1635, 1555, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 2.95 (2H, d, J=7.79Hz), 3.85 (3H, s), 4.22 (2H, br s), 4.67 (1H, dd, J=14.1Hz and

7.5Hz), 6.82 (1H, s), 7.1-8.2 (7H, m), 9.15 (1H, s), 11.77 (1H, br s)

MASS : M^{+1} 326

Preparation 12

To a solution of Starting Compound (2.0 g) in DMF (40 ml) were added methyl iodide (5.09 ml) and powdered potassium carbonate (5.30 g). The mixture was stirred at 75°C for four hours. The mixture was filtered and concentrated under vacuum and water and added to the residue. The crystalline precipitates were collected by filtration, washed with water, and dried at 40°C to give Object Compound (2.94 g).

mp : 94-96°C

IR (Nujol) : 1710, 1520, 875, 850, 800, 767, 733 cm^{-1}

NMR (DMSO-d_6, δ) : 3.87 (3H, s), 4.02 (3H, s), 7.20-7.80 (4H, m)

Preparation 13

To an ice-cooled solution of Starting Compound (2.43 g), N-methylbenzylamine (0.90 ml), and HOBT (0.94 g) in methylene chloride (50 ml), was added WSC·HCl (1.33 g). The solution was stirred at the same temperature for an hour and at room temperature overnight. After evaporation, the reaction mixture was extracted with ethyl acetate, and the organic layer was washed successively with water, and aqueous sodium hydrogencarbonate solution, 0.5N hydrochloric acid, water and an aqueous sodium chloride solution, and was dried over magnesium sulfate. Evaporation gave Object Compound (1.40 g) as a crystalline solid.

mp : 99-103°C

IR (Nujol) : 3370, 1685, 1645, 1515, 1405, 1250, 1170 cm^{-1}

NMR (DMSO-d_6, δ) : 1.15-1.35 (9H, m), 2.75-3.20 (5H, m), 4.40-4.85 (3H, m), 6.95-8.05 (12H, m)

Preparation 14

The object compound was obtained according to a similar manner to that of Preparation 13.

IR ($CHCl_3$) : 3310, 1705, 1640, 1490, 1170 cm^{-1}

NMR (DMSO-d_6, δ) : 1.22 and 1.32 (9H, m), 2.46 (3H, s), 2.75 and 2.85 (3H, s), 2.9-3.1 (2H, m), 4.4-4.8 (3H, m), 6.9-7.8 (12H, m)

Preparation 15

To an ice-cooled solution of Starting Compound (3.08 g) in methylene chloride (30 ml) was added 4N-HCl/DOX (27.5 ml). The solution was stirred at the same temperature for five minutes. Then the cooling bath was removed and the solution was stirred at room temperature for half an hour. After evaporation, the residue was crystallized with diisopropyl ether, and the product was collected by filtration, and dried over sodium hydroxide in vacuo to give Object Compound (2.36 g).

mp : 177-185°C

IR (Nujol) : 3420, 1650, 1600, 1495, 1285 cm^{-1}

NMR (DMSO-d_6, δ) : 2.65 and 2.70 (3H, s), 3.15-3.40 (2H, m), 4.0-4.8 (3H, m), 7.0-8.1 (11H, m), 8.58 (3H, br s)

Preparation 16

The object compound was obtained according to a similar manner to that of Preparation 15.

mp : 170-172°C

IR (Nujol) : 3500-3350, 1650, 1605, 1510, 1450 cm^{-1}

NMR (DMSO-d_6, δ) : 2.47 (3H, s), 2.61 and 2.70 (3H, s), 3.1-3.3 (2H, m), 3.95-4.8 (3H, m), 6.95-7.8 (11H, m), 8.49 (2H, br s)

Preparation 17

To an ice-cooled solution of Starting Compound (1.3 g), Boc-(2S,4R)-Pro(4OH)-OH (0.77 g) and HOBT (0.45 g) in a mixed solvent of methylene chloride (26 ml) was added WSC (0.61 ml). The solution was stirred at the same temperature for an hour and at room temperature overnight. After evaporation, the reaction mixture was extracted with ethyl acetate and the organic layer was washed successively with an aqueous sodium hydrogencarbonate solution, water, 0.5N hydrochloric acid, water and an aqueous sodium chloride solution, and was dried over magnesium sulfate. Evaporation gave the Object Compound (1.88 g) as an amorphous solid.

IR ($CHCl_3$) : 3450-3300, 1695-1650, 1640, 1400 cm^{-1}

NMR (DMSO-d_6, δ) : 1.10-1.40 (9H, m), 1.50-1.80 (1H, m), 1.80-2.10 (1H, m), 2.70-3.30 (7H, m), 4.10-5.20 (6H, m), 6.90-8.0 (11H, m), 8.35-8.50 (1H, m)

Preparation 18

The object compounds were obtained according to a similar manner to that of Preparation 17.

(1) IR ($CHCl_3$) : 3420-3220, 1695, 1680-1660, 1645-1630 cm^{-1}

NMR (DMSO-d_6, δ) : 1.21 and 1.39 (9H, s), 1.6-1.8 (1H, m), 1.8-2.0 (1H, m), 2.40 (3H, s), 2.7-3.5 (7H, m), 4.1-5.2 (6H, m), 6.9-7.8 (11H, m), 8.35-8.5 (1H, m)

(2) IR ($CHCl_3$) : 3300, 1710, 1640, 1485, 1365, 1165 cm^{-1}

NMR (DMSO-d_6, δ) : 1.37 (9H, s), 2.75 and 2.83 (3H, s), 2.90-3.25 (2H, m), 3.43-3.60 (2H, m), 4.20-4.75 and 4.90-5.20 (3H, m), 6.85-7.95 and 8.25-8.40 (14H, m)

(3) IR ($CHCl_3$) : 3300, 1710-1620, 1515-1490, 1450, 1360, 1160 cm^{-1}
NMR (DMSO-d_6, δ) : 1.37 (9H, s), 1.55-1.9 (2H, m), 1.95-2.2 (2H, m), 2.73 and 2.82 (3H, s), 2.9-3.25 (3H, m), 3.85-4.0 (2H, m), 4.3-4.6 (2H, m), 4.9-5.2 (1H, m), 6.7-7.9 (13H, m), 8.3-8.4 (1H, m)

(4) IR ($CHCl_3$) : 3330, 1715, 1635, 1500, 1460, 1170 cm^{-1}
NMR (DMSO-d_6, δ) : 1.38 (9H, s), 2.73 and 2.82 (3H, s), 2.9-3.3 (2H, m), 3.4-3.6 (2H, m), 3.9-5.2 (5H, m), 6.65-7.95 (13H, m), 8.15-8.3 (1H, m)

(5) IR ($CHCl_3$) : 3320, 1720, 1635, 1495, 1460, 1320, 1170 cm^{-1}
NMR (DMSO-d_6, δ) : 1.37 (9H, s), 1.6-1.85 (2H, m), 1.9-2.0 (3H, m), 2.25-2.4 (2H, m), 2.74 and 2.83 (3H, s), 2.95-3.25 (2H, m), 3.9-5.2 (4H, m), 6.9-7.9 (13H, m), 8.26 (1H, d, J=7.92Hz)

(6) IR ($CHCl_3$) : 1700, 1630, 1490, 1390, 1365 cm^{-1}
NMR (DMSO-d_6, δ) : 1.1-1.5 (9H, m), 2.7-3.4 (7H, m), 4.3-5.2 (6H, m), 6.9-7.9 (12H, m), 8.45-8.6 (1H, m)

(7) IR ($CHCl_3$) : 3300, 1710, 1690, 1640 cm^{-1}
NMR (DMSO-d_6, δ) : 1.1-1.55 (6H, m), 1.37 (9H, s), 2.74 and 2.82 (3H, s), 2.85-3.3 (4H, m), 3.9-5.15 (6H, m), 6.7-7.95 (19H, m), 8.35-8.45 (1H, m)

(8) mp : 126.0-127.0°C
IR (Nujol) : 3330, 1710, 1635, 1515, 859, 820 cm^{-1}
NMR (DMSO-d_6, δ) : 1.347 (9H, s), 1.45-1.70 (2H, m), 1.859, 1.902 (3H, s), 2.10-2.35 (2H, m), 2.803,

2.912 (3H, s), 2.90-3.25 (2H, m), 3.90-4.15 (1H, m), 4.379 (J=15.11Hz), 4.515 (J=18.40Hz), 4.600 (J=15.38Hz), 4.726 (J=16.62Hz)(2H, d), 4.95-5.25 (1H, m), 6.830 (J=14.62Hz), 6.887 (J=8.20Hz)(1H, d), 6.95-7.90 (12H, m), 8.383 (J=8.31Hz), 8.496 (J=8.50Hz)(1H, d)

Preparation 19

To an ice-cooled solution of Starting Compound (1.72 g) in methylene chloride (20 ml) was added 4N-HCl/DOX (12.3 ml). The solution was stirred at the same temperature for five minutes and at room temperature for twenty minutes. After evaporation, the residue was triturated with diisopropyl ether, collected by filtration and dried to give Object Compound (1.52 g).

mp : 131°C (dec)~

IR (Nujol) : 3350-3150, 1670, 1640, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.77 and 2.85 (3H, s), 2.9-3.4 (4H, m), 4.2-4.6 and 5.0-5.2 and 5.5-5.65 (6H, m), 7.9-8.05 (11H, m), 8.58 (1H, br s), 9.26 (1H, d, J=7.70Hz), 10.05 (1H, br s)

Preparation 20

The object compounds were obtained according to a similar manner to that of Preparation 19.

(1) IR ($CHCl_3$) : 3350, 1665, 1640, 1490, 1395 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.47 (3H, s), 2.77 and 2.83 (3H, s), 2.95-3.35 (4H, m), 4.2-5.6 (6H, m), 6.9-7.8 (11H, m), 8.6 (1H, br s), 9.23 (1H, d, J=7.6Hz), 9.85 (1H, br s)

(2) IR ($CHCl_3$) : 1680, 1630, 1490-1470, 1450, 1135 cm^{-1}

NMR (DMSO-d_6, δ) : 2.79 and 2.87 (3H, s), 2.90-3.30 (2H, m), 3.40-3.50 (2H, m), 4.20-5.25 (3H, m), 6.80-7.95 (12H, m), 8.18 (3H, br s), 9.00-9.15 (1H, m)

(3) IR ($CHCl_3$) : 3300-3100, 1680-1650, 1640, 1620, 1450 cm^{-1}
NMR (DMSO-d_6, δ) : 1.9-2.05 (2H, m), 2.2-2.35 (2H, m), 2.76 and 2.85 (3H, m), 3.0-3.3 (2H, m), 3.7-3.9 (3H, m), 4.35-5.2 (3H, m), 6.85-7.95 (12H, m), 8.36 (3H, br s), 9.17 (1H, d, J=8.46Hz)

(4) IR ($CHCl_3$) : 3300-3200, 1680, 1630, 1490, 1120 cm^{-1}
NMR (DMSO-d_6, δ) : 2.76 and 2.85 (3H, s), 3.0-3.3 (2H, m), 3.65-3.95 (2H, m), 4.3-5.6 (5H, m), 6.9-7.95 (12H, m), 8.22 (3H, br s), 9.0-9.1 (1H, m)

(5) IR ($CHCl_3$) : 3430-3100, 1675, 1640, 1630, 1545 cm^{-1}
NMR (DMSO-d_6, δ) : 1.95-2.1 (5H, m), 2.45-2.55 (2H, m), 2.76 and 2.85 (3H, s), 3.0-3.3 (2H, m), 3.8-5.2 (4H, m), 6.9-7.95 (12H, m), 8.37 (3H, br s), 9.1-9.2 (1H, m)

(6) mp : 190°C~ (dec.)
IR (Nujol) : 3200, 2700, 1680, 1650, 1555, 1450 cm^{-1}
NMR (DMSO-d_6, δ) : 2.77 and 2.86 (3H, s), 2.95-3.6 (4H, m), 4.2-4.7 (5H, m), 5.0-5.25 (1H, m), 6.9-8.0 (13H, m), 9.28 (1H, d, J=7.5Hz)

Preparation 21

To an ice-cooled solution of Starting Compound (0.50 g) in ethyl acetate (10 ml) was added 4N-HCl/ethyl acetate (20 ml). The solution was stirred at the same temperature

for an hour. After evaporation, the residue was triturated with diethyl ether, collected by filtration, and dried over sodium hydroxide in vacuo to give Object Compound (0.38 g).

IR (Nujol) : 3400, 1678, 1630, 1562, 1546, 815, 730 cm^{-1}

NMR (DMSO-d_6, δ) : 1.74, 1.83, 1.91 (3H, s), 1.55-1.95 (2H, m), 2.00-2.30 (2H, m), 2.86, 2.99 (3H, s), 2.90-3.45 (2H, m), 3.75-3.90 (1H, m), 4.25-4.40, 4.60-4.85 (2H, m), 5.00-5.30 (1H, m), 6.90-7.90 (13H, m), 8.21 (2H, br s), 9.05-9.20 (1H, m)

Preparation 22

Starting Compound (257 g) was dissolved in methanol (50 ml) and 10% palladium on charcoal (0.26 g) was added. The mixture was hydrogenated at room temperature for three and half hours under atmospheric pressure. Then two drops of concentrated hydrochloric acid were added and hydrogenation was continued for an hour. After filtration and evaporation to dryness, Object Compound (1.93 g) was obtained as an amorphous solid.

IR ($CHCl_3$) : 3400-3300, 1710, 1700, 1640, 1370 cm^{-1}

NMR (DMSO-d_6, δ) : 1.1-1.6 (6H, m), 1.37 (9H, s), 2.77 and 2.85 (3H, s), 2.95-3.4 (4H, m), 4.3-5.2 (4H, m), 6.7-7.95 (15H, m), 8.55-8.65 (1H, m)

Preparation 23

To an ice-cooled solution of Starting Compound (315g) and methyl iodide (5.0ml) in THF(30ml) was added 1.20g of 60 % sodium hydride under nitrogen atmosphere. The mixture was stirred at room temperature overnight. Water was added to the mixture and THF was evaporated. Ether and water were added and the aqueous layer was separated. The organic layer was washed with water again. Two aqueous layers were combined and acidified with 6N hydrochloric acid to pH2 and the separated oil was extracted with ethyl acetate. The extract was washed with sodium chloride solution and was dried over magnesium sulfate and evaporated to give Object Compound (2.05g) as a crystalline solid.

IR (Nujol) : 1750,1645cm^{-1}

mp : 135~136.5 ℃

NMR($CDCl_3$, δ) : 1.27and1.36(9H,s), 2.69and2.77(3H,s), 4.74(dd,J=4.3Hz,10.7Hz), 4.98(dd,J=5.2Hz,10.7Hz), 7.3-7.85(7H,m), 9.16(1H, brs)

Preparation 24

The object compound was obtained according to a similar manner to to that of Preparation 13.

IR (Nujol) : 1680,1646cm^{-1}

mp : 122~123 ℃

NMR($CDCl_3$, δ) : 0.96,1.058,1.148 and 1.30(9H,s), 2.85(3H,s),2.90(3H,s),3.0~3.5(2H,m), 4.35~4.8(2H,m) 5.13 and 5.50(1H,m), 6.8~7.8(12H,m)

Elemental Analysis

Calc. : C74.97,H7.46,N6.48

Found : C74.93,H7.70,N6.66

Preparation 25

Starting Compound (2.42g) was dissolved in 15ml of ethyl acetate, and ice-cooled. To this solution was added 4N hydrochloric acid in ethyl acetate(30ml). The solution was

stirred at this temperature for 40minutes and concentrated. To the residue were added methylene chloride (50ml) and saturated sodium hydrogencarbonate aqueous solution and the organic layer was separated. The aqueous layer was extracted with methylene chloride again. The combined extract was washed with brine and dried with magnesium sulfate to give Object Compound .

Preparation 26

The object compound was obtained according to a similar manner to to that of Preparation 25.

mp : 242~243 ℃ (dec)

IR (Nujol) : 1645,1550cm^{-1}

NMR (DMSO-d_6, δ) : 2.49,2.50,2.51,2.54,2.57(6H,s), 3.19(1H,dd,J=13.2Hz,3.5Hz), 3.55(1H,dd,J=13.2Hz, 9.2Hz), 3.99and4.39(J=16.2Hz),4.32and4.55(J=14.7Hz),4.85(1H,m), 6.85~7.94(12H,m), 9.53(2H,brs)

Elemental Analysis

Calc. : C71.63,H6.83,N7.59,C19.61

Found : C71.40,H6.87,N7.57,C19.65

Preparation 27

The object compound was obtained according to a similar manner to to that of Preparation 17.

Preparation 28

A mixture of Starting Compound (4.5g) ethyl bromoacetate (3.01g), and pottasium carbonate (4.97g) in dimethyl formamide (60ml) was stirred at room temperature for three hours. The mixture was filtered, evaporated, diluted in water and extracted with ethyl acetate. The organic layer was washed successively with water, sodium hydrogencarbonate solution, water, 0.5N hydrochloric acid, and brine, and dried over magnesium sulfate. Evaporation gave 6.10g of Object Compound as a crystalline soild.

mp : 73~75.5 ℃

IR (Nujol) : 1748,1690cm^{-1}

NMR($CDCl_3$, δ) : 1.24(3H,t,J=7Hz), 4.21(2H,q,J=7Hz), 4.84(2H,s),5.38(2H,s), 7.24-7.50(8H,m),7.84(1H,s) 8.22(1H,m)

Preparation 29

Starting Compound ester (6.10g) was dissolved in 100ml of ethanol. To this solution was added 0.3ml of 4N hydrochloric acid in dioxane and 0.6g of 10% palladium on charcoal. The mixture was hydrogenated under atmospheric pressure for five hours. The mixture was filtered, concentrated to give 3.58g of Object Compound as a crystalline solid.

mp : 145~146 ℃

IR (Nujol) : 2600,1734,1660,1640cm^{-1}

NMR (DMSO-d_6, δ) : 1.22(3H,d,J=7Hz),4.16(2H,q,J=7Hz), 5.23(2H,s),7.17-7.28(2H,m),7.44-7.52(1H,m),8.0-8.1(1H,m),8.06(1H,s)

Preparation 30

To a solution of Starting Compound (2.51g) and ethyl 4-bromobutyrate (1.95g) was added 0.40g of 60% sodium hydride under ice-cooling. The mixture was stirred at room temperature overnight. The mixture was evaporated, diluted in water, and extracted with ethyl acetate. The organic layer was washed successively with sodium hydrogencarbonate sulution and brine, and dried over magnesium sulfate. After evaporateion, the residue was washed with petroleum ether by decantation to give Object Compound (3.25g) as an oil.

IR (Film) : 1730,1700,1532cm^{-1}

NMR($CDCl_3$, δ) : 1.23(3H,t,J=7Hz),2.2(2H,m),2.3(2H,t,J=7Hz),4.12(2H,q,J=7Hz),4.22(2H,t,J=7Hz),5.38(2H,s), 7.25-7.51(8H,m),7.83(1H,s),8.20(1H,m)

Preparation 31

The object compound was obtained according to a

similar manner to to that of Preparation 29.

mp : 92~93 ℃

IR (Nujol) : 1740,1655cm^{-1}

NMR($CDCl_3$, δ) : 1.25(3H,t,J=7Hz),2.20(3H,t,J=6.5Hz), 2.33(2H,m),4.14(2H,q,J=7Hz),4.25(2H,t,J=6.5Hz), 7.25-7.44(3H,m),7.92(1H,s),8.21-8.3(1H,m)

Preparation 32

The object compound was obtained according to a similar manner to to that of Preparation 30 and used to the next reaction without purification.

Preparation 33

The object compound was obtained according to a similar manner to to that of Preparation 5.

mp : 124.5-125 ℃

IR (Nujol) : 2500,1680,1660,1535cm^{-1}

NMR (DMSO-d_6, δ) : 5.60(2H,s),7.16-7.30(4H,m), 7.5(1H,m),7.75(1H,m),8.05(1H,m),8.24(1H,s), 8.53(1H,m),12.07(1H,m)

Elemental Analysis

Calc. : C68.95,H5.01,N10.72(as0.5H_2O)

Found : C69.43,H5.02,N10.39

Preparation 34

To a solution of Starting Compound (6.1g) in a mixed solvent of acetone and water (1:1,100ml) was added di-tert-butyl-dicarbonate (21.8g) dissolved in acetone (50ml) under ice-cooling. The resulting solution was stirred at room temperature for three hours. Acetone was evaprorated and the product was extracted twice with methylene chloride. The combined extract was washed successively with 0.5N hydrochloric acid and brine, and dried over magnesium sulfate. Evaporation gave Object Compound (16.7g) as an oil.

IR (Film) : 3370,1690,1525cm^{-1}

NMR($CDCl_3$, δ) : 1.45(9H,s),3.28(2H,t,J=5Hz),3.69(2H,t, J=5Hz)

Preparation 35

To a solution of Starting Compound (16.7g) and triethylamine (12.63g) in 140ml of methylene chloride was added methanesulfonyl chloride (12.6g) at -20 ℃ in twenty minutes. The resulting mixture was stirred at 0 ℃ for an hour. The solution was washed successively with water, 0.5N hydrochloric acid, and brine, and dried over magnesium sulfate. Evaporation gave Object Compound (22.34g), as an oil, which was kept in freezer to prevent decomposition.

IR (Film) : 3410,1700,1520,1350cm^{-1}

NMR($CDCl_3$, δ) : 1.45(9H,s),3.15(3H,s),3.46(2H,m),9.29(2H,t,J=5.2Hz),4.93(1H,s,br)

Preparation 36

The object compound was obtained according to a similar manner to to that of Preparation 28 and used to the next reaction without purification.

Preparation 37

The object compound was obtained according to a similar manner to to that of Preparation 29.

mp : 185~186.5 ℃ (dec)

IR (Nujol) : 3450,1680,1650cm^{-1}

NMR (DMSO-d_6, δ) : 1.31(9H,s),3.32(2H,m),4.27(2H,t, J=6Hz),6.97(1H,t,J=5.5Hz),7.2(2H,m), 7.55-7.6(1H,m),7.99(1H,s),8.0(1H,m),11.94(1H,s)

Elemental Analysis

Calc. : C63.14,H6.62,N9.20

Found : C61.68,H6.70,N8.93

Preparation 38

The object compound was obtained according to a

similar manner to to that of Preparation 13.

IR ($CHCl_3$) :3320,1740,1700,1650,1500,1450cm^{-1}

NMR (DMSO-d_6, δ) : 1.1-1.3(12H,m),2.85-3.15(2H,m),3.9-4.9(7H,m),7.15-7.9(13H,m)

MASS : M^+ 490

Preparation 39

The object compound was obtained according to a similar manner to to that of Preparation 15.

IR ($CHCl_3$) :3400,1745,1665,1605,1490,1470,1455cm^{-1}

NMR (DMSO-d_6, δ) : 1.18(3H,t,J=7.1Hz),3.2-3.45(2H,m), 3.65-4.85(7H,m),7.1-8.0(12H,m),8.51(3H,br-s)

Preparation 40

The object compound was obtained according to a similar manner to to that of Preparation 17.

IR ($CHCl_3$) : 3420-3300,1750,1700-1645,1500,1450, 1400cm^{-1}

NMR (DMSO-d_6, δ) : 1.0-1.15(9H,m),1.3-1.4(3H,m), 1.5-1.7(1H,m),1.8-2.0(1H,m),2.9-3.4(4H,m),3.95-5.1(10H,m),6.9-8.0(12H,m),8.4-8.6(1H,m)

Preparation 41

A mixture of Starting Compound (4.9g), ethyl bromoacetate (1.69g) cetyltrimethylammonium chloride (0.32g) , and powdered sodium hydroxide (1.84g) in 100ml of methylene chloride was stirred at room temperature for three days. The mixture was filtered through a pad of powdered cellulose. The filtrate was concentrated, diluted in water, and extracted with ethyl acetate. The organic layer was washed successively with sodium hydrogencarbonate solution, water, 1N hydrochloric acid, water, and and brine, and dried over magnesium sulfate. After evaporation, the crude product was purified on a silica gel column (150g) eluting with a mixed solvent of chloroform and methanol (50:1) to

give Object Compound (2.86g) as an amorphous solid.

IR ($CHCl_3$) : 3300,1755,1700,1640,1400cm^{-1}

NMR (DMSO-d_6, δ) : 1.15-1.25(9H,m),1.29(3H,s),1.6-1.8(1H,m) 2.05-2.3(1H,m),2.7-3.25(5H,m),3.4-3.5(2H,m), 4.0-5.2(9H,m),6.85-7.9(12H,m),8.4-8.5(1H,m)

MASS : M$^+$ 617

Preparation 42

The object compounds were obtained according to a similar manner to to that of Preparation 19.

(1) IR ($CHCl_3$) : 3370-3200,1740,1650,1550,1440,1200cm^{-1}

NMR (DMSO-d_6, δ) : 1.17(3H,t,J=7.15Hz),1.7-1.9(1H,m), 2.15-2.35(1H,m),2.95-3.4(4H,m),4.0-5.2(10H,m),7.0-8.0(12H,m),8.57(1H,br-s),9.25-9.4(1H,m), (1H,m),9.81(1H,br-s)

(2) IR ($CHCl_3$) : 3450,3200,1750,1680,1640,1560,1450cm^{-1}

NMR (DMSO-d_6, δ) : 1.21(3H,t,J=7.1Hz),1.7-1.95(1H,m), 2.45-2.65(1H,m),2.77and2.85(3H,s), 3.0-3.45(4H,m),4.05-5.2(9H,m),6.85-7.95 (12H,m),8.7(1H,br-s),9.2-9.3(1H,m), 10.25(1H,br-s)

Example 1

To an ice-cooled solution of 1-methylindole-3-carboxylic acid (0.47 g), Starting Compound (1.35 g) and HOBT (0.36 g) in 25 ml of methylene chloride was added WSC (0.49 ml). The solution was stirred at the same temperature for an hour and at room temperature overnight. After evaporation, the reaction mixture was extracted with

ethyl acetate and the organic layer was washed successively with an aqueous sodium hydrogencarbonate solution, water, 0.5N hydrochloric acid, water, and an aqueous sodium chloride solution, and dried over magnesium sulfate. After evaporation, the residue was purified on a silica gel column (50 g) eluting with a mixed solvent of chloroform and methanol (30:1). The fractions containing the desired compound were collected and evaporated to give Object Compound (1.15 g) as an amorphous solid .

IR ($CHCl_3$) : 3450-3270, 1650, 1635, 1435, 1420 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-1.9 (1H, m), 1.9-2.1 (1H, m), 2.72 and 2.82 (3H, s), 2.95-3.3 (2H, m), 3.6-4.0 (2H, m), 3.85 (3H, s), 4.2-5.15 (6H, m), 6.9-8.1 (16H, m), 8.45-8.6 (1H, m)

Example 2

The object compounds were obtained according to a similar manner to that of Example 1.

(1) mp : 126°C~ (dec.)

IR (Nujol) : 3420, 3270, 1660, 1630, 1605, 1535, 1320, 1245 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-1.9 (1H, m), 1.9-2.1 (1H, m), 2.46 (3H, s), 2.70 and 2.78 (3H, s), 2.9-3.25 (2H, m), 3.6-3.75 (2H, m), 3.85 (3H, s), 4.2-5.15 (6H, m), 6.85-8.1 (16H, m), 8.4-8.55 (1H, m)

(2) IR ($CHCl_3$) : 3300, 1630, 1540, 1465, 1275, 1125 cm^{-1}

NMR (DMSO-d_6, δ) : 2.78 and 2.86 (3H, s), 2.95-3.30 (2H, m), 3.83 (3H, s), 3.85-3.95 (2H, m), 4.20-5.25 (3H, m), 6.85-8.20 (18H, m), 8.40-8.60 (1H, m)

(3) IR (Nujol) : 3275, 1635, 1548, 740 cm^{-1}

NMR (DMSO-d_6, δ) : 1.89, 1.94 (3H, s), 1.50-2.00

(2H, m), 2.20-2.45 (2H, m), 2.81, 2.94 (3H, s), 2.90-3.30 (2H, m), 3.82 (3H, s), 4.30-4.85 (3H, m), 4.95-5.25 (1H, m), 6.90-7.90 (16H, m), 8.12 (1H, s), 8.14 (1H, d, J=7.70Hz), 8.52, 8.65 (1H, d, J=8.18Hz and 8.60Hz)

(4) mp : 158-160°C
IR (Nujol) : 3550, 3300, 1690, 1675, 1595, 1530, 1240 cm^{-1}
NMR (DMSO-d_6, δ) : 1.8-2.0 (2H, m), 2.1-2.3 (2H, m), 2.75 and 2.84 (3H, m), 2.9-3.3 (2H, m), 3.84 (3H, s), 4.05-5.2 (4H, m), 6.75-8.6 (19H, m)

(5) mp : 108-113°C
IR (Nujol) : 3460, 3330, 1625, 1540, 1240 cm^{-1}
NMR (DMSO-d_6, δ) : 2.73 and 2.84 (3H, s), 2.95-3.3 (2H, m), 3.6-3.75 (2H, m), 3.85 (3H, s), 4.25-5.25 (5H, m), 6.85-8.5 (19H, m)

(6) IR ($CHCl_3$) : 3300, 1640, 1630, 1540, 1380, 1280, 1120 cm^{-1}
NMR (DMSO-d_6, δ) : 1.8-2.0 (2H, m), 2.01 (3H, s), 2.4-2.55 (2H, m), 2.75 and 2.85 (3H, s), 3.0-3.3 (2H, m), 3.84 (3H, s), 4.3-5.2 (4H, m), 6.9-8.5 (19H, m)

(7) IR ($CHCl_3$) : 3300, 1710, 1690, 1640-1620, 1365 cm^{-1}
NMR (DMSO-d_6, δ) : 1.2-1.75 (6H, m), 1.62 (9H, s), 2.74 and 2.84 (3H, s), 2.9-3.3 (4H, m), 3.84 (3H, s), 4.35-5.2 (4H, m), 6.7-8.5 (20H, m)

Example 3

To a suspended mixture of diphenylacetic acid (424.5 mg) and HOBT (270 mg) in methylene chloride (15 ml) was added WSC·HCl (382 mg) at room temperature. The solution

was stirred at the same temperature for an hour. To the solution were added Starting Compound (1.09 g), and TEA (0.417 g) and the solution was stirred at room temperature overnight. After concentration, the residue was extracted with ethyl acetate, the organic layer was washed successively with saturated sodium hydrogencarbonate solution, water, 0.5N hydrochloric acid, and sodium chloride solution, and dried over magnesium sulfate. After concentration, the residue was crystallized by addition of ether, and collected by filtration to give Object Compound (1.12 g).

mp : 200-202°C

IR (Nujol) : 3400, 1695, 1645, 1630, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-2.2 (2H, m), 2.77 and 2.85 (3H, s), 3.0-3.3 (2H, m), 3.3-3.6 (2H, m), 4.2-4.6 (4H, m), 4.9-5.3 (2H, m), 6.7-7.9 (23H, m), 8.48 (d, J=8Hz) and 8.97 (m)(1H)

Example 4

The object compounds were obtained according to a similar manner to that of Example 3.

(1) mp : 197.0-200.5°C

IR (Nujol) : 3400, 3310, 3130, 1678, 1643, 1578, 1530, 745 cm^{-1}

NMR (DMSO-d_6, δ) : 1.60-2.25 (2H, m), 2.57, 2.73, 2.82 (3H, s), 2.90-3.45 (2H, m), 3.75, 3.82 (3H, s), 3.50-3.95 (2H, m), 3.95-5.25 (6H, m), 6.55-8.00 (16H, m), 8.50-8.75 (1H, m)

(2) mp : 98°C~ (dec.)

IR (Nujol) : 3430-3220, 1630, 1600, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 1.6-2.1 (6H, m), 2.4-3.3 (11H, m), 3.6-4.0 (2H, m), 4.2-5.2 (8H, m), 6.8-8.15 (17H, m), 8.45-8.75 (1H, m)

(3) IR ($CHCl_3$) : 3410, 1640, 1605, 1395 cm^{-1}
NMR (DMSO-d_6, δ) : 1.75-1.9 (1H, m), 1.9-2.1 (1H, m), 2.19 (6H, s), 2.6-2.75 (4H, m), 2.80 (3H, s), 3.0-3.3 (2H, m), 3.6-4.05 (2H, m), 4.25-5.20 (6H, m), 6.85-8.1 (17H, m), 8.5-8.65 (1H, m)

Example 5

To an ice-cooled solution of indoline (238 mg) in methylene chloride (8 ml) was added trichloromethyl chloroformate (0.12 ml). The mixture was stirred for an hour at room temperature, and pyridine (0.16 ml) was added, and the mixture was stirred further for an hour and was ice-cooled. Then, Starting Compound (818 mg) and TEA (0.21 ml) was added at the same temperature and the mixture was stirred five hours at room temperature during which period TEA (0.10 ml) was added. After evaporation, the residue was extracted with ethyl acetate and the organic layer was washed successively with sodium hydrogen carbonate solution, 0.5N hydrochloric acid, and sodium chloride solution, and was dried over magnesium sulfate. After evaporation, the crude product was purified on a silica gel column chromatography (20 g) eluting with chloroform-methanol (2%) to give Object Compound (480 mg) as an amorphous solid.

IR (Nujol) : 3400, 3300, 1640, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.6-1.85 (1H, m), 1.95-2.2 (1H, m), 2.71 and 2.80 (3H, s), 2.9-4.0 (8H, m), 4.2-4.7 (4H, m), 4.9-5.2 (2H, m), 6.8-7.9 (16H, m), 8.4 (1H, m)
MASS : M^+ 576

Example 6

Starting Compound I (1.0 g) was suspended in DMF (20 ml). The solution was cooled to -15°C and 4N-HCl/DOX (1.53 ml) was added. To the resulting solution was added

tert-butyl nitrite (0.35 ml) at the same temperature and the solution was stirred for twenty minutes, and TEA (0.86 ml) was added. In another reaction vessel was prepared a solution of Starting Compound II (0.99 g) and TEA (0.43 ml) in DMF (10 ml). This solution was added to the former reaction mixture at -20°C and the solution was stirred at -10°C for an hour and at 0°C for three hours. The reaction mixture was poured into water (150 ml) and the pH was adjusted to 8 with sodium hydrogen carbonate solution. The product was extracted with ethyl acetate and the organic layer was washed sodium hydrogen carbonate solution and sodium chloride solution, and dried with magnesium sulfate. After evaporation, the crude product was purified on a silica gel column chromatography eluting with chloroform-methanol (30:1 to 20:1) to give Object Compound (1.41 g).

IR ($CHCl_3$) : 3300, 1695-1680, 1500, 1270, 1125 cm^{-1}

NMR (DMSO-d_6, δ) : 2.74 and 2.81 (3H, s), 2.85-3.25 (4H, m), 3.84 (3H, s), 4.2-5.2 (4H, m), 6.8-8.5 (21H, m), 11.79 (1H, br s)

Example 7

To a solution of Starting Compound (1.0 g) and TEA (0.59 ml) in methylene chloride (20 ml) was added indole-3-carbonyl chloride (0.41 g) under ice-cooling. The solution was stirred at the same temperature for three hours and at room temperature overnight. After evaporation, the reaction mixture was extracted with ethyl acetate and the organic layer was washed successively with an aqueous sodium hydrogencarbonate solution, water, 0.5N hydrochloric acid, water, and an aqueous sodium chloride solution, and dried over magnesium sulfate. After evaporation, the residue was purified on a silica gel column (65 g) eluting with a mixed solvent of chloroform and methanol (30:1). The fractions containing the desired

compound were collected and evaporated to give Object Compound (1.0 g) as an amorphous solid.

IR ($CHCl_3$) : 3350-3250, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 2.76 and 2.86 (3H, s), 2.95-3.3 (4H, m), 3.80 and 3.83 (3H, s), 4.3-4.75 (3H, m), 5.0-5.25 (3H, m), 6.9-8.0 (17H, m), 8.65-8.75 (1H, m)

Example 8

To an ice-cooled solution of Starting Compound (0.86 g) in methylene chloride (18 ml) was added 4N-HCl/ethyl acetate (16 ml). The solution was stirred at the same temperature for thirty minutes. Then the cooling bath was removed and the solution was stirred at room temperature for an hour. After evaporation, the residue was triturated with diethyl ether, collected by filtration, and dried over sodium hydroxide in vacuo to give crude material (0.87 g). This material was separated between sodium hydrogencarbonate solution and methylene chloride. The organic layer was washed with water and dried over magnesium sulfate. After evaporation, the residue was dissolved in methylene chloride (5 ml) and 4N-HCl/DOX (0.153 ml) was added. After evaporation, the residue was dried under vacuum to give Object Compound (0.36 g) as an amorphous solid.

IR ($CHCl_3$) : 3450-3200, 1660, 1645, 1635-1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.1-1.8 (6H, m), 2.65-3.3 (4H, m), 2.74 and 2.84 (3H, s), 3.84 (3H, s), 4.3-5.2 (4H, m), 6.9-8.5 (22H, m)

Example 9

Starting Compound (0.50 g) was dissolved in THF (10 ml) and 4N-HCl/DOX (0.39 ml) was added at room temperature. Methylene chloride (10 ml) was added to dissolve the separated oil and the solution was stirred

for thirty minutes. After evaporation, the residue was triturated with diisopropyl ether, filtered, and dried to give Object Compound (0.53 g) as an amorphous solid.

IR ($CHCl_3$) : 3450-3250, 1660, 1645, 1635 cm^{-1}

NMR (DMSO-d_6, δ) : 1.75-2.15 (2H, m), 2.7-3.35 (11H, m), 3.45-4.2 (5H, m), 4.3-5.2 (7H, m), 6.85-8.15 (17H, m), 8.5-8.65 (1H, m)

Example 10

To a solution of Starting Compound (1.73g) in 25ml methylene chloride were added triethylamine (0.707g) and trimethylacetyl chloride (0.844g) under ice-cooling and the resulting solution was stirred at this temperature for fifteen minutes. The solution was added to a mixture of the amine trifluoroaetate (3.82g) and triethylamine (0.707g) in 35ml of methylene chloride under ice-cooling. The mixture was stirred at the temperature for an hour and at room temperature overnight. Triethylamine (0.35ml) was added to the mixture and the solution was stirred for additional six hours. The reaction mixture was washed successively with water, diluted sodium hydrogencarbonate solution, 0.5N hydrochloric acid ,and brine, and dried over magnesium sulfate. After evaporation, the crude material was purifried on a silica-gel column (80g) eluting with a mixed solvent of chloroform and methanol(from 98:8 to 96.5:3.5) to give Object Compound (2.70g) as an amorphous solid.

NMR (DMSO-d_6, δ) : 1.22(3H,t,J=7Hz),1.7-2.1(2H,m), 2.72 and 2.81(3H,s),3.0-3.2(2H,m),3.6-4.0(2H,m), 4.17(2H,q,J=7Hz),4.2-4.6(3H,m),4.7(1H,m),5.0-5.25(3H,m,),5.23(2H,s),6.8-8.1(17H,m),8.56(1H,m,)

Example 11

To a solution of Starting Compound (2.70g) in 50ml of ethanol was added dropwise a mixture of 1N sodium hydroxide (4.1ml) and ethanol (5ml) at room temperature. The mixture

was stirred for one and half an hour. After ethanol was evaporated, the resulting solution was diluted with water and extracted once with ether. The acqueous layer was separated, acidified to pH1 with 1N hydrochloric acid, and extracted twice with methylene chloride. The combined extract was washed with brine and dried over magnesium sulfate. Evaporation gave 2.20g of Object Compound (2.20g) as an amorphous solid.

IR (Nujol) : 1730,1620,3300cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-2.1(2H,m),2.71 and 2.81(3H,s), 3.1-3.5(2H,m),3.65 and 3.9(2H,m),4.3-4.6(2H,m),4.72(1Ht,J=7Hz),5.05(2H,m),5.12(2H,s),6.8-8.2(18H,m), 8.6(1H,m)

Example 12

A mixture of Starting Compound (654mg), 3,5-dimethylpyrazole-1-carboxamidine nitrate (201ml), and triethylamine (202ml) was stirred at room temerature overnight. Triethylamine (145mg) and 3,5-dimethylpyrazole-1-carboxamidine nitrate (402mg) were added and the mixture was stirred for additional four days. The mixture was concentrated, diluted with water and the pH was adjusted to 4 with 1N hydrochloric acid. The solution was extracted twice with a mixed solvent of chloroform and n-butanol(4:1). The combined extract was evaported and the residue was triturated with ethyl acetate, filtered, and dried to give Object Compound (680mg) as an amorphous solid.

IR (Nujol) : 3350,3200,1635,1530cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.2(2H,m),2.73 and 2.80(3H,s), 3.0-3.3(2H,m),3.5-3.75(3H,m),3.9(1H,m),4.3-4.8(6H, m),5.1(2H,m),6.9-7.3(10H,m),7.4-7.6(5H,m),7.7-7.95 (5H,m),8.1(1H,m),8.56(1H,m)

MASS(FAB) : M+H$^+$ 660

Example 13

To an ice-cooled solution of N-benzylmethylamine (0.50g) in 20ml of methylene chloride was added trimethyl chloroformate(0.41g). After stirring at room temperature for an hour, pyridine (0.32g) was added to the mixture. The reaction mixture was stirred for additional two hours. Thereto Starting Compound (1.69g) and triethylamine(0.47g) were added amd the mixture was stirred at room temperature overnight, during which period 4-dimethylaminopyridine(0.50g) was added to complete the reaction. The mixture was concentrated, diluted in water, and extracted with ethyl acetate. The organic layer was successively washed with sodium hydrogencarbonate solution water, 0.5N hydrochloric acid, water, and brine, and dried over magnesium sulfate. After evaporation, the crude product was purified on silica gel column (50g) eluting with a mixed solvent of chloroform and methanol (20:1) to give Object Compound (1.17g) as an amorphous solid.

IR ($CHCl_3$) : 3450-3300,1710,1700,1490,1450,1400cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.7(1H,m),1.8-2.0(1H,m),2.63(3H, m),2.77and2.85(3H,s),2.9-3.3(2H,m),3.5-3.7(2H,m), 4.1-5.3(8H,m),6.8-8.2(17H,m) 8.8-8.9(1H,m)

MASS : M^+ 578

Example 14

To a solution of Starting Compound (1.97g) in 40ml of ethanol was added 1N sodium hydroxide (2.69g). The solution was stirred at room temperature for two hours. After ethanol was evaporated, water and ethyl acetate were added and the aqueous layer was separated The pH was adjusted to 5 with 1N hydrochloric acid and the solution was left standing overnight. The resulting precipitates were collected by filtration,washed with water, and dried to give Object Compound (1.60g).

IR (Nujol) : 3470,3150,1650,1595,1540,1400,1230cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.0(1H,m),2.1-2.3(1H,m),2.23(6H,

s),2.6-2.9(5H,m),3.0-3.3(2H,m),3.8-5.2(12H,m),
6.85-8.1(17H,m),8.5-8.7(1H,m)

Example 15

To a solution of Starting Compound (4.69g) in 47ml of methylene chloride was added triethylamine (1.44g) and methanesulfonyl chloride (0.814g) The resulting mixture was stirred at the temperature for three hours, in which period methanesulfonyl chloride (0.82g) and triethylamine (1.44g) were added. The solution was washed with water and the organic layer was dried over magnesium sulfate. This crude product was purified on a silica gel column (162g) eluting with a mixed solvent of chloroform and methanol (40:1) to give Object Compound (4.77g) an amorphous solid.

IR ($CHCl_3$) : 3300,1750,1680,1630,1530,1360,1180cm^{-1}

NMR (DMSO-d_6, δ) : 1.1-1.25(3H,m),2.0-2.2(1H,m),2.3-2.6 (1H,m),2.73and2.78(3H,s),3.22(3H,s), 3.0-3.3(2H,m),3.8-5.4(11H,m),6.85-8.1(17H,m),8.4-8.8(1H,m)

Example 16

A solution of Starting Compound (4.73g) and sodium azide(0.83g) in dimethylsulfoxide (25ml) was heated at 70 ℃ overnight. After cooling, ethyl acetate (100ml) and water (100ml) were added. The organic layer was separated and washed with water (twice) and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated to 50ml volume. To this solution was added triphenyl phosphine (1.68g) and the mixture was stirred at 50℃ for three hours. Then water (0.35ml) was added and the mixture was stirred at 65 ℃ for additional five hours. After evaporation, the residual oil was applied to a silica gel column (150g) eluted with a mixed solvent of chloroform and methanol (10:1 to 4:1, gradient elution) to give Object Compound (3.11g).

IR ($CHCl_3$) : 3200,1750,1630,1540,1490,1420,1200cm^{-1}

NMR (DMSO-d_6, δ) : 1.1-1.3(3H,m),1.5-1.7(1H,m),2.25-2.45(1H,m),2.65-2.85(3H,m),3.0-3.5(6H,m),3.7-5.3(9H,m),6.8-8.1(17H,m),8.5-8.8(1H,m)

MASS(FAB) : 660.2$(M+1)^+$,682.3$(M+Na)^+$

Example 17

The object compounds were obtained according to a similar manner to to that of Example 1.

(1) mp : 196~200 ℃

IR (Nujol) : 3450,1660(sh),1640,1590,1575,1530cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-2.2(2H,m),2.71and2.76(3H,s),2.8-3.0(1H,m),3.5-3.6(1H,m),3.18and3.23(3H,s),3.7-4.0(2H,m),3.85and3.86(3H,s),4.3-4.6(3H,m),5.1(3H,m),5.7(1H,m),6.8-8.2(17H,m)

Elemental Analysis

Calc. : C73.61,H6.51,N9.28

Found : C73.45,H6.44,N9.12

(2) IR (Nujol) : 1640cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-2.3(2H,m),2.71and2.74(3H,s),2.8-3.0(1H,m),3.13and3.18(3H,s),3.4-3.8(3H,m),4.3-4.6(3H,m),4.8-5.0(1H,m),5.4and5.6-5.8(2H,m),6.8-8.0(14H,m),8.85(2H,m),9.30(1H,m)

(3) IR ($CHCl_3$) : 3450,3300,1660,1600,1510,1450,1280cm^{-1}

NMR (DMSO-d_6, δ) : 1.6-2.4(4H,m),2.7-2.9(5H,m),2.9-3.8(10H,m),4.1-5.2(6H,m),6.5-7.9(14H,m),8.4-8.5(1H,m),8.7-8.9(1H,m)

MASS : M^+ 623

(4) IR ($CHCl_3$) : 3270,1740,1650,1600,1530,1470,1200cm^{-1}

NMR (DMSO-d_6, δ) : 1.0-11(3H,m),1.65-2.1(2H,m),2.19(6H,s)2.6-2.7(2H,m),2.8-3.3(2H,m),3.6-5.1(14H,m),6.9-

8.1(17H,m),8.4-8.6(1H,m)

MASS(FAB) : 718.3$(M+1)^+$,740.3$(M+Na)^+$

(5) IR ($CHCl_3$): 3320,1755,1630,1530,1460,1430,1210,1130cm^{-1}

NMR (DMSO-d_6, δ) : 1.16(3H,t,J=7.1Hz),1.75-1.95(1H,m), 2.19(6H,s),2.05-2.35(1H,m),2.5-2.9(5H,m),3.0-3.3(2H,m),3.75-5.20(13H,m),6.85-8.15 (17H,m),8.5-8.7(1H,m)

MASS(FAB) : 732.5$(M+1)^+$,754.4$(M+Na)^+$

Example 18

The object compounds were obtained according to a similar manner to to that of Example 10.

(1) IR (Nujol) : 3430,3300,1732,1650(sh),1630,1605cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-2.1(3H,m),1.14(3H,t,J=7Hz),2.29 (2H,t,J=7Hz),2.71and2.81(3H,s),3.0-3.3(2H,m),3.65(1H,m),3.9(1H,m),4.02(2H,q,J=7Hz),4.2-4.55(5H,m), 4.71(1H,m),5.0-5.2(2H,m),6.87-8.07(17H,m),8.54(1H, m)

Elemental Analysis

Calc. : C69.67,H6.56,N7.93

Found : C69.54,H6.56,N7.83

(2) mp : 184~187 ℃ (dec)

IR (Nujol) : 3400,3300,1660,1625,1600cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-2.1(2H,m),2.71and2.81(3H,s),3.0- 3.3(2H,m),3.7 and 3.97(2H,m),4.2-4.6(3H,m), 4.73(1H,m),5.0-5.2(2H,m),5.61(2H,s),6.8-7.9(1H,m), 8.11(2H,brs),8.55(2H,m)

Elemental Analysis

Calc. : C73.96,H5.90,N10.52

Found : C72.83,H5.88,N10.10

(3) mp : 115~120 ℃
IR (Nujol) : 3430,3300,1710,1655,1630,1600cm^{-1}
NMR (DMSO-d_6, δ) : 1.74 and 1.35(9H,s),1.7-2.1(2H,m),
2.71 and 2.80(3H,s),3.0-3.3(2H,m),3.3(2H,m),
3.7 and 3.9(2H,m),4.2-4.6(5H,m),4.7(1H,m),
5.0-5.2(2H,m),6.8-7.9(17H,m),8.06(1H,d,J=8Hz),
8.53(1H,m)
Elemental Analysis
Calc. : C70.27,H6060,N9076
Found : C69.19,H6.61,N9.57

(4) IR ($CHCl_3$) : 3450-3300,1750,1640,1535,1190cm^{-1}
NMR (DMSO-d_6, δ) : 1.22(3H,t,J=7.06Hz),1.65-2.15(2H,m),
2.71and2.81(3H,s),2.9-3.3(2H,m),3.34(2H,s),3.5-
5.3(10H,m),6.8-8.15(17H,m),8.45-8.6(1H,m)
MASS(FAB) : 661.3$(M+1)^+$,683.2$(M+Na)^+$

Example 19

The object compounds were obtained according to a similar manner to to that of Example 11.

(1) IR (Nujol) : 3400-3300,1720,1630cm^{-1}
NMR (DMSO-d_6, δ) : 1.7-2.1(3H,m),2.22(2H,m),2.71 and
2.81(3H,s),3.0-3.3(2H,m),3.64-3.69(1H,m),3.92(1H,
m),4.2-4.5(5H,m),4.71(1H,m),4.9-5.2 (2H,m),6.9-8.1
(17H,m),8.54(1H,m),12.2(1 H,br)

(2) IR (Nujol): 3420,3260,1650-1590,1530,1310,1260,1200cm^{-1}
NMR (DMSO-d_6, δ) : 1.8-2.0(1H,m),2.4-2.6(1H,m),2.70 and
2.73(3H,s),2.9-3.3(2H,m),3.7-5.2(12H,m),6.8-8.1(
17H,m),8.8-9.0(1H,m)
MASS(FAB) : 632.3$(M+1)^+$,654.2$(M+Na)^+$

Example 20

The object compound was obtained according to a

similar manner to to that of Preparation 19.

MASS(FAB):M+H$^+$ 618.3

Example 21

The object compound was obtained according to a similar manner to to that of Example 11.

IR (Nujol) : 3400-3200,1640,1600,1550,1200cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-1.9(1H,m),1.9-2.1(1H,m),2.24 and 2.26(6H,s),2.7-3.3(4H,m),3.6-5.1(12H,m),7.0-8.1(18H,m),8.60(1H,br-s)

Example 22

The object compound was obtained according to a similar manner to to that of Example 13.

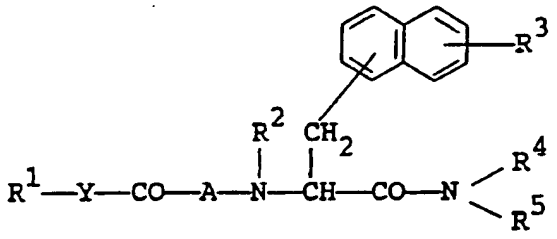
IR ($CHCl_3$) : 3450-3300,1640,1480,1390,1200cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.7(1H,m),1.8-2.0(1H,m),2.65-2.85(6H,m),3.0-3.7(4H,m),3.80(3H,s),4.05-5.3(8H,m),6.8-8.2(16H,m),8.8-8.9(1H,m)

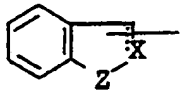
MASS : M$^+$ 608

CLAIMS

1. A compound of the formula :



wherein R^1 is lower alkyl, aryl, ar(lower)alkyl, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, or a group of the formula :



wherein the symbol of a line and dotted line is a single bond or a double bond,

X is CH or N, and

Z is O, S or NH,

each of which may have suitable substituent(s);

R^2 is hydrogen or lower alkyl;

R^3 is hydrogen or suitable substituent;

R^4 is lower alkyl which may have suitable substituent(s), and

R^5 is ar(lower)alkyl which may have suitable substituent(s) or pyridyl(lower)alkyl,

or

R^4 and R^5 are linked together to form

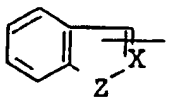
benzene-condensed lower alkylene;

A is an amino acid residue which may have suitable substituent(s); and

Y is bond, lower alkylene, lower alkenylene, or lower alkylimino,

provided that when

R^1 is aryl, or a group of the formula :



wherein X is as defined above, and

Z is O or $N-R^6_a$,

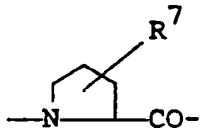
in which R^6_a is hydrogen or lower alkyl,

R^2 is hydrogen,

R^4 is lower alkyl which may have suitable substituent(s),

R^5 is ar(lower)alkyl which may have suitable substituent(s),

A is a group of the formula :



wherein R^7 is hydroxy or lower alkoxy, and

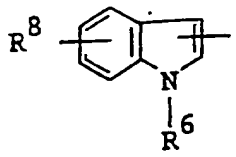
Y is bond or lower alkenylene, then

R^3 is suitable substituent,

and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R^1 is di(lower)alkoxyphenyl, mono-or di-or triphenyl-(lower)alkyl which may have lower alkoxy, indolinyl, pyridyl, or a group of the formula :



whrein R^6 is lower alkyl, di(lower)alkylamino(lower)-alkyl, pyrrolidinyl(lower)alkyl, carboxy-(lower)alkyl, esterified carboxy(lower)-alkyl, amino(lower)alkyl, guanidino(lower)-alkyl, pyridyl(lower)alkyl or acylamino-(lower)alkyl, and

R^8 is hydrogen or halogen,

R^3 is lower alkyl or halogen,

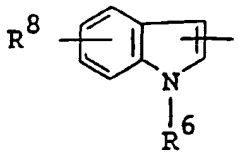
R^4 is lower alkyl, carboxy(lower)alkyl or esterified carboxy(lower)alkyl.

R^5 is mono-or di-or triphenyl(lower)alkyl or pyridyl(lower)-alkyl, and

A is a bivalent residue derived from an amino acid selected from the group consisting of hydroxyproline, glycine, serine, methionine, lysine, histidine, glutamine, thioproline and aminoproline, whose side chains may be substituted by the substituent selected from the group consisting of lower alkoxycarbonyl, carboxy(lower)alkyl, esterified carboxy(lower)alkyl and lower alkylsulfonyl.

3. A compound of claim 2, wherein

R^1 is a group of the formula :



wherein R^6 is lower alkyl, and

R^8 is hydrogen,

R^2 is hydrogen,

R^4 is lower alkyl,

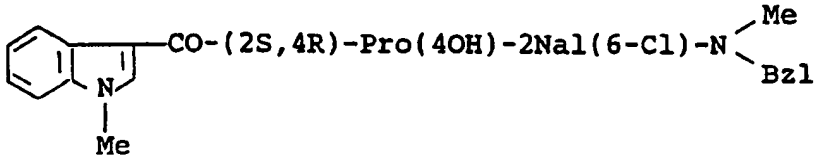
R^5 is phenyl(lower)alkyl,

A is a bivalent residue derived from hydroxyproline, and

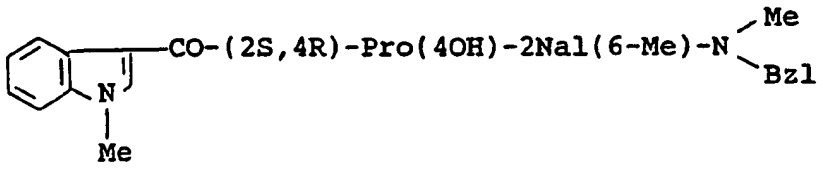
Y is bond.

4. A compound of claim 3, which is selected from the group consisting of :

(1)

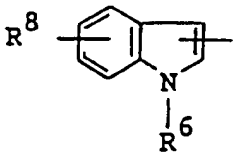


(2)



5. A compound of claim 1, wherein.

R^1 is di(lower)alkoxyphenyl, mono-or di-or triphenyl-(lower)alkyl which may have lower alkoxy, indolinyl, pyridyl, or a group of the formula :



whrein R^6 is lower alkyl, di(lower)alkylamino(lower)-

alkyl, pyrrolidinyl(lower)alkyl, carboxy-(lower)alkyl, esterified carboxy(lower)-alkyl, amino(lower)alkyl,guanidino(lower)-alkyl, pyridyl(lower)alkyl or acylamino-(lower)alkyl, and

R^8 is hydrogen or halogen,

R^3 is hydrogen,

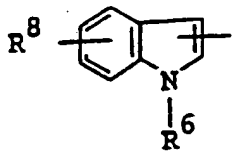
R^4 is lower alkyl, carboxy(lower)alkyl or esterified carboxy(lower)alkyl.

R^5 is mono-or di-or triphenyl(lower)alkyl, and

A is a bivalent residue derived from an amino acid selected from the group consisting of glycine, serine, methionine, lysine, histidine, glutamine, thioproline and aminoproline, whose side chains may be substituted by the substituent selected from the group consisting of lower alkoxycarbonyl, carboxy(lower)alkyl, esterified carboxy(lower)alkyl and lower alkylsulfonyl.

6. A compound of claim 5, wherein

R^1 is a group of the formula :



wherein R^6 is lower alkyl, and

R^8 is hydrogen,

R^2 is hydrogen,

R^4 is lower alkyl,

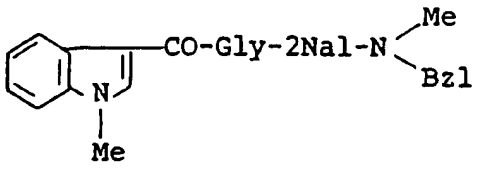
R^5 is phenyl(lower)alkyl,

A is a bivalent residue derived from an amino acid selected from the group consisting of glycine, serine, methionine, lysine, histidine, glutamine and thioproline, and

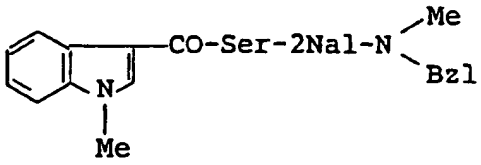
Y is bond.

7. A compound of claim 6, which is selected from the group consisting of :

(1)



(2)



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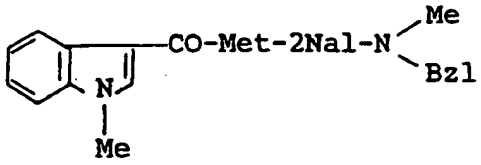
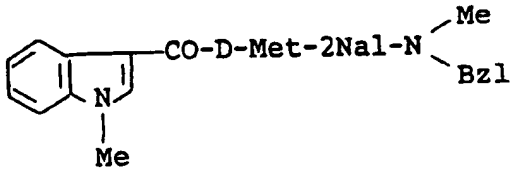
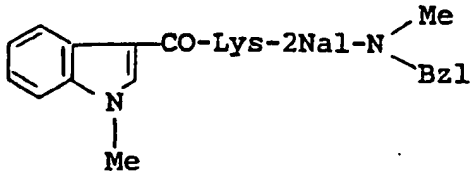


(4)

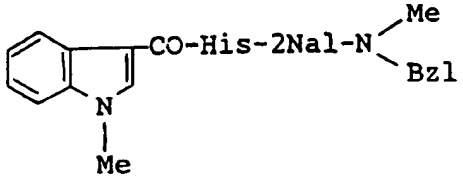


(5)

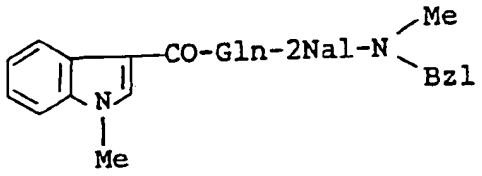


or its hydrochloride

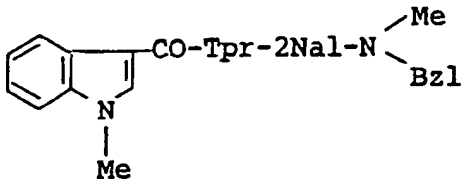
(6)



(7)

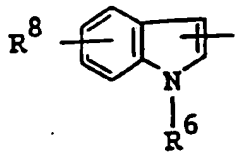


(8)



8. A compound of claim 1, wherein.

R^1 is di(lower)alkoxyphenyl, mono-or di-or triphenyl-(lower)alkyl which may have lower alkoxy, indolinyl, pyridyl, or a group of the formula :



whrein R^6 is lower alkyl, di(lower) alkylamino(lower) alkyl, pyrrolidinyl-(lower)alkyl, carboxy(lower)alkyl, esterified carboxy(lower)alkyl, amino-(lower)alkyl,guanidino(lower)alkyl, pyridyl(lower)alkyl or acylamino(lower)-alkyl, and

R^8 is hydrogen or halogen,

R^3 is hydrogen,

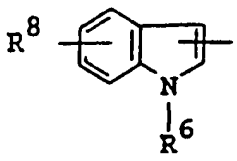
R^4 is lower alkyl, carboxy(lower)alkyl or esterified carboxy(lower)alkyl.

R^5 is mono-or di-or triphenyl(lower)alkyl, and

A is a bivalent residue derived from hydroxyproline which may be substituted by the substituent selected from the group consisting of carboxy(lower)alkyl, esterified carboxy(lower)alkyl and lower alkylsulfonyl.

9. A compound of claim 8, wherein

R^1 is di(lower)alkoxyphenyl, diphenyl(lower)alkyl, indolinyl, pyridyl, or a group of the formula :



whrein R^6 is di(lower)alkylamino(lower)alkyl, pyrrolidinyl(lower)alkyl, carboxy(lower)-alkyl, amino(lower)alkyl, guanidino(lower)-alkyl or pyridyl(lower)alkyl, and

R^8 is hydrogen,

R^4 is lower alkyl or carboxy(lower)alkyl,

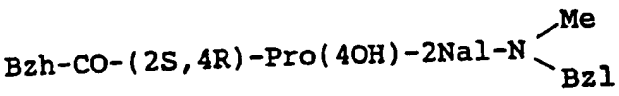
R^5 is phenyl(lower)alkyl,

A is a bivalent residue derived from hydroxyproline which may be substituted by carboxy(lower)alkyl, and

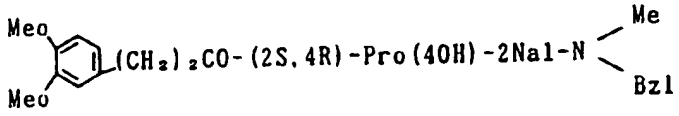
Y is bond, lower alkylene or lower alkenylne.

10. A compoound of claim 9, which is selected form the group consisting of :

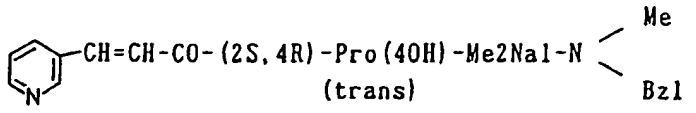
(1)



(2)

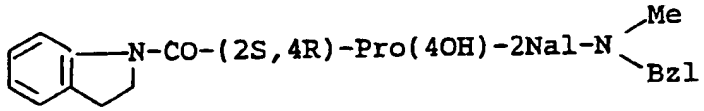


(3)

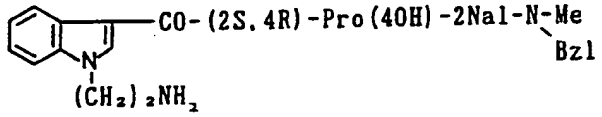


or its hydrochloride

(4)

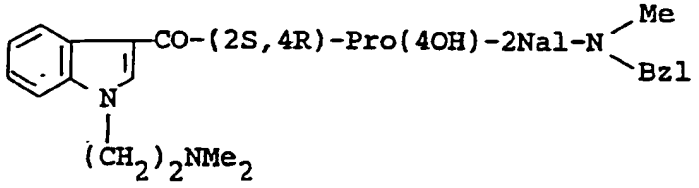


(5)



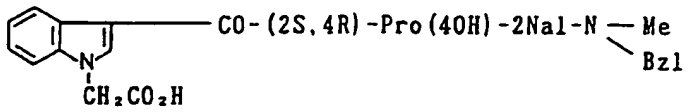
or its hydrochloride

(6)



or its hydrochloride

(7)



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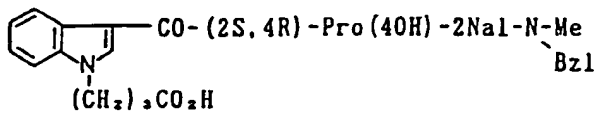

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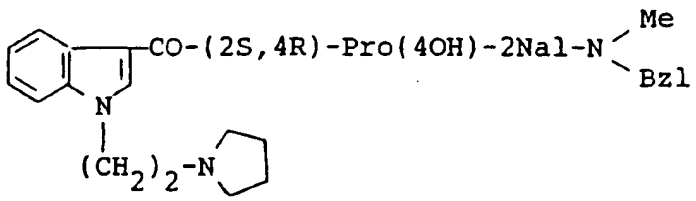
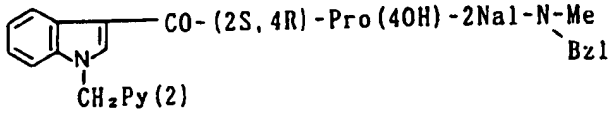
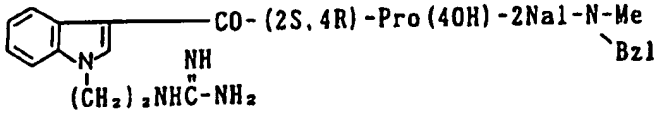


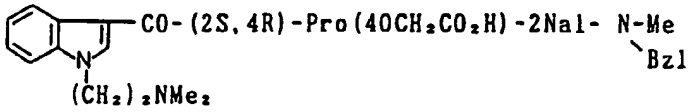
(10)



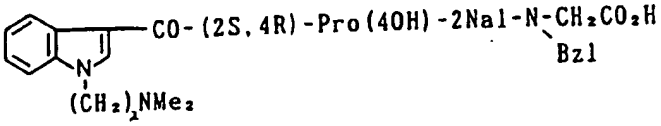
(11)



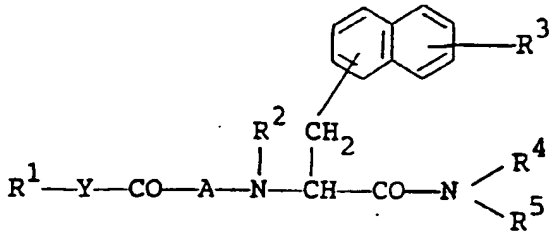
(12)



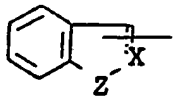
(13)



11. A process for preparing a compound of the formula :



wherein R^1 is lower alkyl, aryl, ar(lower)alkyl, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, or a group of the formula :



wherein the symbol of a line and dotted line is a single bond or a double bond,

X is CH or N, and

Z is O, S or NH,

each of which may have suitable substituent(s);

R^2 is hydrogen or lower alkyl;

R^3 is hydrogen or suitable substituent;

R^4 is lower alkyl which may have suitable substituent(s), and

R^5 is ar(lower)alkyl which may have suitable substituent(s) or pyridyl(lower)alkyl, or

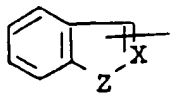
R^4 and R^5 are linked together to form benzene-condensed lower alkylene;

A is an amino acid residue which may have suitable substituent(s); and

Y is bond, lower alkylene, lower alkenylene or lower alkylimino,

provided that when

R^1 is aryl, or a group of the formula :



wherein X is as defined above, and

Z is O or N-R^{6a},

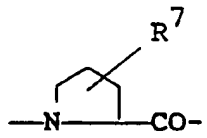
in which R^{6a} is hydrogen or lower alkyl,

R^2 is hydrogen,

R^4 is lower alkyl which may have suitable substituent(s),

R^5 is ar(lower)alkyl which may have suitable substituent(s),

A is a group of the formula :



wherein R^7 is hydroxy or lower alkoxy, and

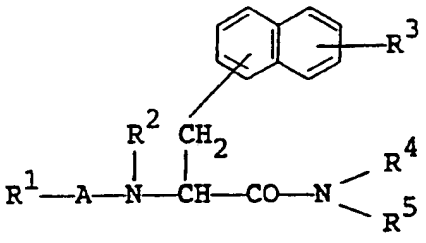
Y is bond or lower alkenylene, then

R^3 is suitable substituent,

or a pharmaceutically acceptable salt thereof,

which comprises

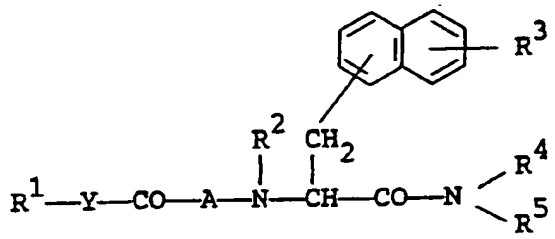
(1) reacting a compound of the formula :



wherein R^2, R^3, R^4, R^5 and A are each as defined above,
or its reactive derivative at the amino group
or a salt thereof, with a compound of the formula :

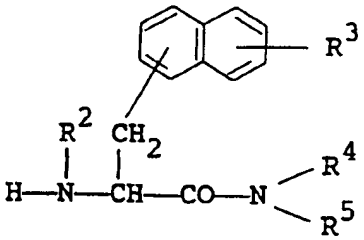
$$R^1 - Y - COOH$$

wherein R^1 and Y are each as defined above,
or its reactive derivative at the carboxy group
or a salt thereof, to give a compound of the formula:



wherein R^1, R^2, R^3, R^4, R^5, A and Y are each as defined above,
or a salt thereof, or

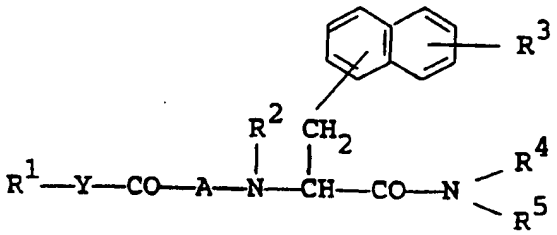
(2) reacting a compound of the formula :



wherein R^2, R^3, R^4, and R^5 are each as defined above,
or its reactive derivative at the amino group
or a salt thereof, with a compound of the formula :

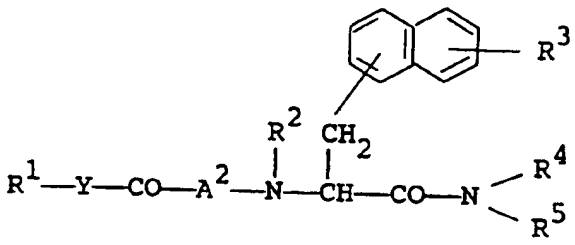
$$R^1\text{-}Y\text{-}CO\text{-}A\text{-}OH$$

wherein R^1, A and Y are each as defined above,
or its reactive derivative at the carboxy group
or a salt thereof, to give a compound of the formula:



wherein R^1, R^2, R^3, R^4, R^5, A and Y are each as defined above,
or a salt thereof, or

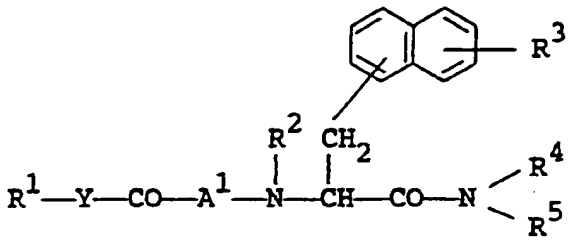
(3) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, and Y are each as defined above,

A^2 is an amino acid residue containing a protected amino, a protected hydroxy and/or a protected carboxy,

or a salt thereof, to elimination reaction of the amino, hydroxy and/or carboxy protective group, to give a compound of the formula :

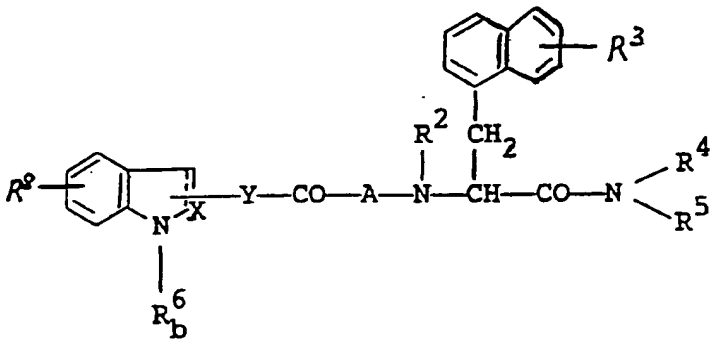


wherein R^1, R^2, R^3, R^4, R^5 and Y are each as defined above, and

A^1 is an amino acid residue containing an amino, a hydroxy and/or a carboxy,

or a salt thereof, or

(4) subjecting a compound of the formula :

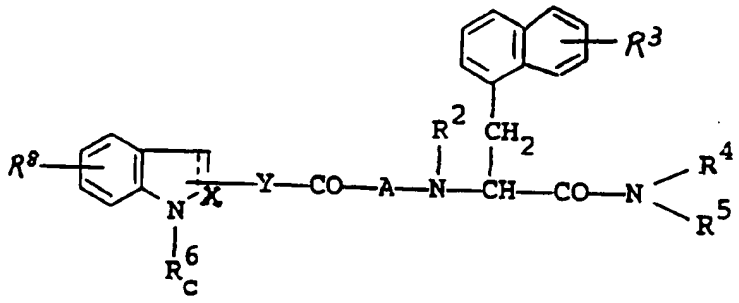


wherein R^2, R^3, R^4, R^5, A, X and Y are each as defined above,

R^{6}_{b} is protected carboxy(lower)alkyl or protected amino(lower)alkyl, and

R^8 is hydrogen or halogen,

or a salt thereof, to elimination reaction of the carboxy or amino protective group, to give a compound of the formula :

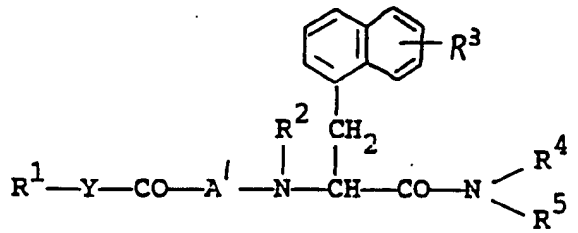


wherein R^2, R^3, R^4, R^5, R^8, A ,X any Y are each as defined above, and

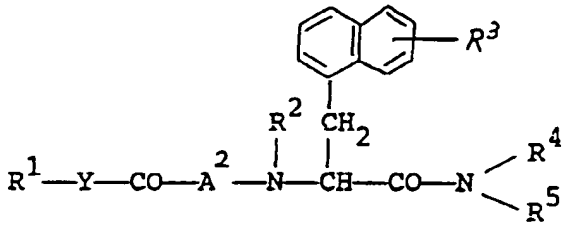
R^{6}_{c} is carboxy(lower)alkyl or amino(lower)alkyl,

or a salt thereof, or

(5) subjecting a compound of the formula :

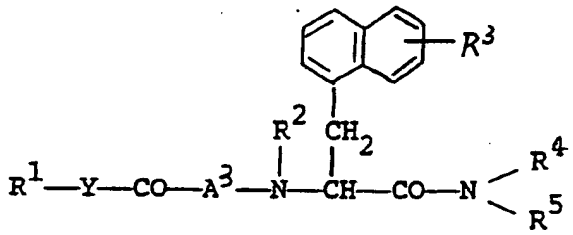


wherein R^1, R^2, R^3, R^4, R^5, A^1 and Y are each as defined above, or its reactive derivative at the amino, hydroxy and/or carboxy group or a salt thereof, to introduction reaction of the amino, hydroxy and/or carboxy protective group, to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, A^2 and Y are each as defined above, or a salt thereof, or

(6) reacting a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5 and Y are each as defined above, and

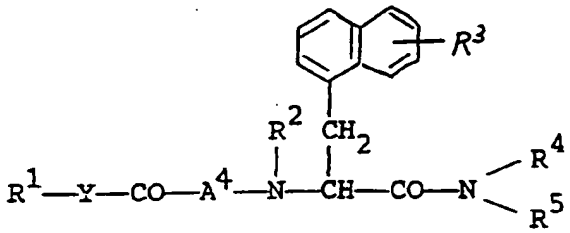
A^3 is an amino acid residue containing a sulfonyloxy which has a suitable substituent,

or a salt thereof, with a compound of the formula :

$$MaN_3$$

wherein Ma is an alkaline metal,

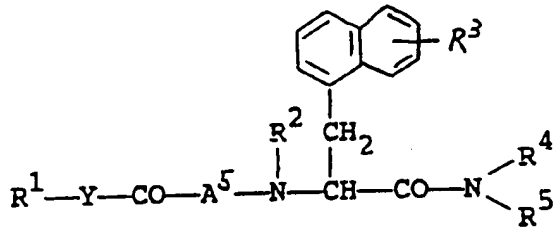
to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5 and Y are each as defined above, and

A^4 is an amino acid residue containing an azido,

or a salt thereof, and successively subjecting the above compound to hydrogenation, to give a compound of the foumula :

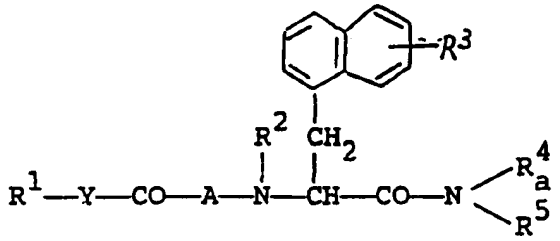


wherein R^1, R^2, R^3, R^4, R^5 and Y are each as defined above, and

A^5 is an amino acid residue containing an amino,

or a salt thereof, or

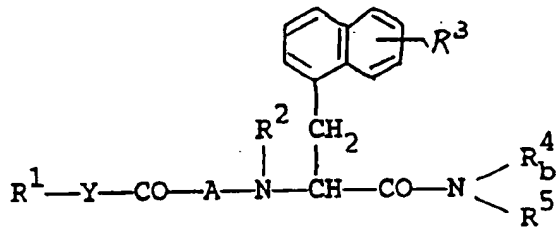
(7) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^5, A and Y are each as defined above, and

R^{4a} is protected carboxy(lower)alkyl,

or a salt thereof, to elimination reaction of the carboxy protective group, to give a compound of the formula :

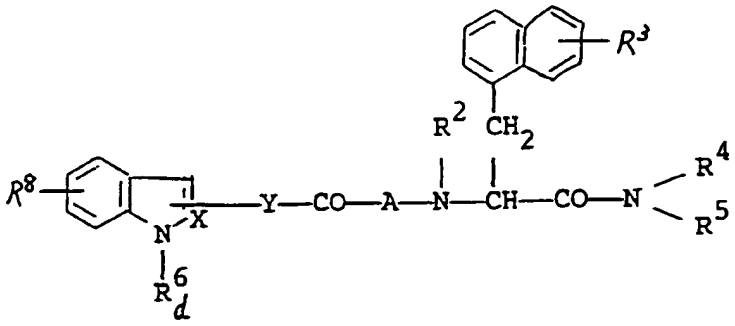


wherein R^1, R^2, R^3, R^5, A and Y are each as defined above, and

R^{4b} is carboxy(lower)alkyl,

or a salt thereof, or

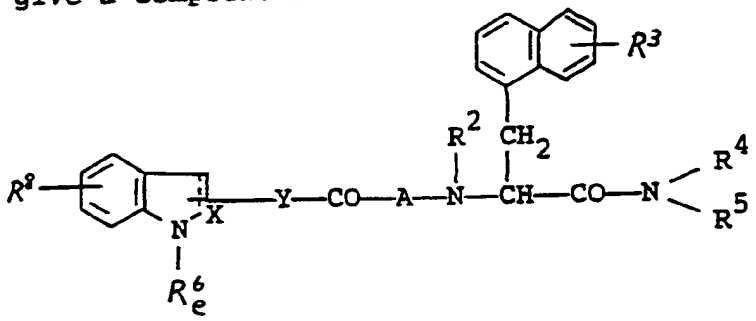
(8) subjecting a compound of the formula :



wherein R^2, R^3, R^4, R^5, R^8, A, X and Y are each as defined above, and

R^{6}_{d} is amino(lower)alkyl,

or a salt thereof, to introduction reaction of amidino group, to give a compound of the formula :



wherein R^2, R^3, R^4, R^5, R^8, A, X and Y are each as defined above, and

R^{6}_{e} is guanidino(lower)alkyl,

or a salt thereof.

12. A pharmaceutical composition which comprises a compound of claim 1 and a pharmaceutically acceptable carrier or excipient.

13. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 with a pharmaceutically acceptable carrier or excipient.

14. A use of a compound of claim 1 as a medicament.

15. A use of a compound of claim 1 as a tachykinin antagonist.

16. A use of a compound of claim 1 as a substance P antagonist.

17. A use of a compound of claim 1 for manufacturing a medicament for treating tachykinin mediated diseases.

18. A method for treating tachykinin mediated diseases which comprises administering a compound of claim 1 to human or animals.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 92/00780

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K5/06; A61K37/43

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 394 989 (FUJISAWA PHARMACEUTICAL CO.,LTD) 31 October 1990 * See Description and examples at pages 38-69 *	1-18
A	EP,A,0 099 057 (BASF AKTIENGESELLSCHAFT) 25 January 1984 * See page 1, line 35 - page 2, line 15 *	1-18
A	ACTA CHEMICA SCANDINAVICA vol. B40, 1986, COPENHAGEN, DENMARK pages 295 - 302; FOLKERS ET AL: 'Design and synthesis of antagonists of substance P' * See page 297, Table 1, Compound 32 * * See page 301-302, Discussion *	1-18

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 AUGUST 1992	09. 09. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	KORSNER S.E.

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 92/00780

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 18 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 9200780 SA 60744

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 28/08/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0394989	31-10-90	JP-A- 3027399	05-02-91
EP-A-0099057	25-01-84	DE-A- 3226241	26-01-84
		CA-A- 1257748	18-07-89
		DE-A- 3374066	19-11-87
		JP-A- 59031746	20-02-84
		US-A- 4610817	09-09-86